Segmentation and quantitative analysis in whole-body PET imaging

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Chapter 3

Variability and repeatability of quantitative uptake metrics in [^{18}F]FDG PET/CT imaging of non-small cell lung cancer: impact of segmentation method, uptake interval and reconstruction protocol

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ABSTRACT

There is increased interest in various new quantitative uptake metrics beyond SUV in oncology PET/CT studies. The purpose of this study was to investigate the variability and test-retest ratio (TRT) of metabolically active tumor volume (MATV) measurements and several other new quantitative metrics in non-small cell lung cancer using [^{18}F]FDG PET/CT with different segmentation methods, user interactions, uptake intervals, and reconstruction protocols.

Methods: Ten patients with advanced non-small cell lung cancer received two whole-body [^{18}F]FDG PET/CT scans at both 60 and 90 min post-injection. PET data were reconstructed with 4 different protocols. Eight segmentation methods were applied to delineate lesions with and without a tumor mask. MATV, SUV_{max}, SUV_{mean}, total lesion glycolysis, and intralesional heterogeneity features were derived. Variability and repeatability were evaluated using a generalized-estimating-equation statistical model with Bonferroni adjustment for multiple comparisons. The statistical model, including interaction between uptake interval and reconstruction protocol, was applied individually to the data obtained from each segmentation method.

Results: Without masking, none of the segmentation methods could delineate all lesions correctly. MATV was affected by both uptake interval and reconstruction settings for most segmentation methods. Similar observations were obtained for the uptake metrics SUV_{max}, SUV_{mean}, total lesion glycolysis, homogeneity, entropy, and zone percentage. No effect of uptake interval was observed on TRT metrics, while the reconstruction protocol affected the TRT of SUV_{max}. Overall, segmentation methods showing poor quantitative performance in one condition showed better performance in other (combined) conditions. For some metrics, a clear statistical interaction was found between the segmentation method and both uptake interval and reconstruction protocol.

Conclusions: All segmentation results need to be reviewed critically. MATV and other quantitative uptake metrics, as well as their TRT, depend on segmentation method, uptake interval, and reconstruction protocol. To obtain quantitative reliable metrics, with good TRT performance, the optimal segmentation method depends on local imaging procedure, the PET/CT system or reconstruction protocol. Rigid harmonization of imaging procedure and PET/CT performance will be helpful in mitigating this variability.

Key Words: Variability, repeatability, segmentation method, non-small cell lung cancer, positron emission tomography imaging

PET imaging with [^{18}F]FDG is extensively used in oncology for diagnosis, staging, prognosis and response monitoring. Various quantitative metrics in PET imaging, such as metabolically active tumor volume (MATV), SUV, and intralesional uptake heterogeneity, have been developed as indicators to quantify glucose metabolism in malignant tumors (1,2). However, the variability in segmentation techniques, user interaction during the segmentation, and imaging acquisition protocols present particular challenges for consistently and accurately obtaining quantitative metrics.

Over the last 20 years, several segmentation methods have been developed and investigated in different tumor types, presenting large variability in terms of delineation accuracy and user interaction (3,4). As reported by the American Association of Physicists in Medicine (AAPM, Report No. 211), validation for most published segmentation methods is either insufficient or inconsistent (5). Besides, although repeatability of quantitative metrics in PET imaging has been extensively explored (6,7), several recent studies have presented conflicting results. Tixier et al. (8) reported poor repeatability of various textural features in esophageal cancer with only a few features being sufficiently reliable. However, van Velden et al. (9) found that most metrics had similar or better repeatability than SUV in non-small-cell lung cancer (NSCLC). It is unclear whether these apparently conflicting results are caused by differences in tumor types, segmentation methodologies, applied imaging protocols, or a combination of all these factors. The systematic comparison of the performances of a range of oncologic image-derived PET metrics obtained using different segmentation methods and imaging protocols is highly desirable.

Therefore, to understand the potential interactions among these aspects, we studied the variability of a representative set of frequently used quantitative metrics for NSCLC PET imaging as a function of segmentation method, user interaction, uptake interval, and reconstruction protocol, along with the repeatability of these metrics.

MATERIALS AND METHODS

Patients

We reanalyzed PET/CT scans from a prospective single-center study on 10 patients with advanced NSCLC who underwent double [^{18}F]FDG PET/CT scans at VU University Medical Center. Patient characteristics are listed in Table 1 and were previously described (9). All patients gave written informed consent before enrolment. This study was approved by the Medical Ethics Review Committee of the VU University Medical Center and was registered in the Dutch trial register (trialregister.nl, NTR3508).

Data Acquisition and Reconstruction

Patients fasted for at least 6 hours before administration of [^{18}F]FDG. All scans were performed using a Ingenuity TF PET/CT scanner (Philips Healthcare). Two whole-body (i.e. skull vertex to mid-thigh) PET/CT scans at 60 and 90 min post-injection were performed. For each PET scan, a low-dose CT scan (120 kVp, 50 mAs) was also obtained. The same procedure was repeated within 3 days after the first examinations. For 2 patients, the 90 min PET scans were not collected because the patients could not comply with the long duration of the scan.

All PET images were reconstructed using 4 different protocols with necessary corrections (e.g., attenuation, scatter, random, normalization), which included a vendor provided body reconstruction protocol (ING), an EANM Research Ltd (EARL)-compliant reconstruction (10), a post-reconstruction resolution model with 1 iteration (PSF1), and the same protocol with 2 iterations (PSF2). The matrix size of all reconstructed images was 144×144 with an isotropic voxel size of 4 mm (supplemental data, available at http://jnm.snmjournals.org).

Delineation Methods

Lesions were identified by a nuclear physician. For each lesion, 8 automated segmentation methods were applied (Supplemental Table 1): a method for automated segmentation using an active contour model (MASAC) (11), an affinity propagation algorithm (AP) (12), a contourlet-based active contour algorithm (CAC) (13), the contrast-oriented thresholding method (ST) of Schaefer et al. (14), segmentation using 41% of the maximum tumor value as a threshold (41MAX) (15), segmentation using 50% of the peak tumor value as a threshold, adapted for local background (A50P) (15), segmentation using an SUV=2.5 as a threshold (SUV25), and segmentation using an SUV=4.0 as a threshold (SUV40).

Each segmentation method was applied with and without a manually defined tumor mask, restricting the region growing to remain within the mask.

Performance Evaluations

The index “out-of-mask” (OM) was included as a metric of segmentation failure:

$$OM=100\times N_{outside}/N_{total} \qquad \text{Eq (1)}$$

where $N_{outside}$ is the number of cases for which the segmentation method without a mask generated a segmentation expanding beyond the predefined tumor mask, and N_{total} is the total number of PET tumor segmentations.

Thus, the OM index reflects the ability of a segmentation method to automatically segment the tumor without spatial constraints (i.e. without a mask). The lower the number, the more successful the method was to generate a tumor segmentation without the inclusion of non-lesioned [^{18}F]FDG-avid areas, or without mislocalization of the segmentation (e.g. “jumping” to a wrong location, such as a different tumor, kidney, bladder, myocardium, or liver).

Quantitative Uptake Metrics

The quantitative metrics evaluated in this study were MATV, SUV_{max}, SUV_{mean}, total lesion glycolysis (TLG), and several textural intratumor heterogeneity features. These features included a global heterogeneity indicator (i.e. area under the curve of the cumulative intensity histogram, CIH_{AUC}) (16), and some local heterogeneity features, such as homogeneity, entropy, dissimilarity, high-intensity emphasis (HIE), and zone percentage (ZP). These features were selected because of their reproducibility and robustness (8,16,17). MATV, SUV_{max}, SUV_{mean}, TLG, and CIH_{AUC} were calculated with in-house software, while local heterogeneity features were obtained with the Pyradiomics package (18). All features were extracted from the original images, without the application of any postprocessing (e.g. rebinning or filtering). Detailed information about the implementation of these metrics are presented in Supplemental Equations 1-5).

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Repeatability Evaluations

Repeatability of the metrics between the 2 scans was calculated as the test-retest ratio (TRT_{metric}) :

$$TRT_{metric}=(Metric_{scan1}- Metric_{scan2})/[(Metric_{scan1}+ Metric_{scan2})/2] \quad \text{Eq (2)}$$

where $Metric_{scan1}$ and $Metric_{scan2}$ are the metric values obtained from the first and second scan, respectively.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics 24.0 software (IBM). The generalized-estimating-equation (GEE) model was used to account for repeated measurements and missing data. The independent working correlation matrix was selected for analysis, with an identity link function. The natural log transformation was applied to MATV, SUV_{max}, SUV_{mean}, TLG, and HIE to obtain normally distributed data.

To assess the influence of uptake interval and reconstruction protocol, the specific metric was selected as the dependent outcome in the GEE model; the patient, scan, uptake interval, and reconstruction protocol were included as independent variables, along with the interaction effect between uptake interval and reconstruction. Similar settings were also used for the TRT_{metric}, excluding the 'scan' variable. A posthoc pairwise comparison was performed when the test of model effect was shown to be significant, applying Bonferroni correction for multiple comparisons present in the test. *P*-values less than 0.05 were considered to be significant.

To explore the relationship between MATV and the other metrics, MATV was set as the dependent outcome, with each other metric included independently as the main effect in the GEE model, and corrected for other factors such as patient, scan, uptake interval, reconstruction protocol, interaction of the uptake interval with the metric, interaction of the reconstruction protocol and the metric, and interaction of uptake interval, reconstruction protocol and the metric. Similarly, the correlation between TRT_{MATV} and TRT of the other metrics was also investigated. Moreover, scatterplots were also used to explore the relationships of TRT_{MATV} with MATV and SUV_{max}.

RESULTS

Tumor Mask

For 41MAX, A50P, SUV25, and SUV40, the use of a mask resulted in significantly smaller (12% - 22%) MATV, whereas CAC showed significantly larger (35%) MATV with masking (Fig. 1). However, applying a tumor mask did not improve the MATV's repeatability in most segmentation results (Fig. 2). Similar results were also found with the other reconstruction protocols.

As shown in Table 2, A50P displayed fewer incorrect segmentation results (30%) compared with the other segmentation methods. In general, CAC and SUV25 showed the worst OM index results (CAC: 77% at 60 min, SUV25: 86% at 90 min). Because no segmentation method correctly delineated all lesions without a mask, we used the results derived from the segmentation with a tumor mask for further analysis.

Uptake Interval and Reconstruction Protocol

Overall, MATV at 90 min uptake interval was larger than at 60 min for CAC, A50P, SUV25, and SUV40, but smaller for MASAC, AP, ST, and 41MAX (Fig. 3), specially affecting those protocols with lower spatial resolution (EARL and ING). These observed differences were statistically significant for all methods, with the exception of MASAC, CAC, and A50P (Table 3 and Supplemental Table 2). For example, direct comparison (i.e. without log transformation) of MATV in EARL reconstructed data showed a median increase of 7% (interquartile range, 1%-13%) for A50P, SUV25 and

SUV40 delineations versus a median decrease of -4% (interquartile range, -8% to 2%) for MASAC, AP, CAC, ST, and 41MAX. In addition, except for SUV40, most segmentation methods showed slightly smaller MATV with reconstruction protocols that provided higher spatial resolutions (in the ascending order EARL, ING, PSF1, and PSF2) at both uptake intervals.

With each segmentation method, SUV_{max}, SUV_{mean}, TLG, entropy, and ZP increased significantly (P<0.001) from 1% to 6% at 90 min uptake interval as compared with 60 min interval. In CAC, homogeneity was independent of uptake interval, whereas all other segmentation methods showed significantly lower homogeneity (2%, P<0.001) at 90 min than at 60 min (Table 3 and Supplemental Table 2).

SUV_{max}, SUV_{mean}, TLG, homogeneity, entropy, and ZP were significantly affected by the reconstruction protocol regardless of the segmentation method. For most segmentation methods, SUV_{max}, SUV_{mean}, entropy, and ZP increased from 1% to 6% at reconstruction protocols with higher spatial resolution, whereas CIH_{AUC} and homogeneity decreased slightly (1%) in these cases (Supplemental Table 3). Compared with other metrics, dissimilarity and HIE were hardly affected by either uptake interval or reconstruction protocol.

There were significant interaction effects for homogeneity; that is, it correlated not only with uptake interval and reconstruction protocol but also with their combinations. For most segmentation methods, the PSF2 reconstruction protocol at 90 min uptake showed the lowest homogeneity, whereas the EARL protocol showed the highest homogeneity at 60 min, except for ST and 41MAX.

Repeatability: Effect of Uptake Interval and Reconstruction Protocol

Uptake interval had no effect on TRT for any metric or segmentation method, whereas the used reconstruction protocol affected TRT in SUV_{max} for each segmentation method (Fig. 4 and Table 4). In general, the TRT in SUV_{max} was worse with higher spatial resolution reconstruction protocols. There were no evident interactions between uptake interval and reconstruction protocol for any of the metrics and segmentation methods.

Relationship Between MATV and Other Metrics as Well as Their Repeatability

There was a significant relationship between MATV and other metrics (Supplemental Table 7). Similarly, TRT_{MATV} strongly correlated with TRT for SUV_{mean}, TLG, CIH_{AUC}, and ZP (Supplemental Table 8). These relationships were also affected by the different uptake intervals and the reconstruction protocols.

Relationship Between TRT_{MATV} and MATV or SUV_{max}

For most segmentation methods, the repeatability of MATV was better at larger MATV and higher SUV (Figure 5 and 6, respectively). A similar trend for the relationship between TRT_{MATV} and MATV or SUV_{max} was also observed at other uptake intervals and for other reconstructions.

DISCUSSION

Our study showed that segmentation methods are influenced by different user interactions, uptake intervals, and reconstruction protocols, suggesting that all segmentation results need to be reviewed critically. User interaction during the segmentation process is often required in medical imaging (19,20). In our study no segmentation method could delineate all lesions correctly without a tumor mask, indicating the necessity of manually defining a tumor mask, especially for tumors adjacent to high activity areas.

In our study, MASAC, CAC, and A50P were statistically independent of the uptake interval (i.e. 60 vs. 90 min) in MATV, whereas SUV25 and SUV40 showed larger MATV at 90 min than at 60 min after [^{18}F]FDG administration (6% and 10%, respectively). Because lesional uptake was higher at 90 than at 60 min, these 2 segmentation methods, taking the absolute SUVs as threshold values, tend to generate larger MATV at 90 min, as occurred in our experiments. However, 41MAX, using relative thresholds, show a slight decrease in MATV at an increased uptake interval. Moreover, MATV obtained with most segmentation methods depends on the reconstruction protocol, and thus, these methods require careful consideration when used in different clinical scenarios.

It has been reported that intralesional heterogeneity correlates with treatment outcome (21). However, regardless of the uncertainties in segmentation methods, differences in acquisition protocols also result in changes in image quality, thus influencing the results for these extracted features (22,23). We found that intralesional heterogeneity increases with uptake interval or spatial image resolution (in ascending order: EARL, ING, PSF1, and PSF2), presented as the decrease in CIH_{AUC} and homogeneity and the increase in entropy and ZP, although dissimilarity and HIE showed less association with uptake interval or reconstruction. The lower the CIH_{AUC} or homogeneity, the higher the heterogeneity of the image, whereas the higher the entropy or ZP, the more details an image carries and the more heterogeneous are the tumor features in the image. Similar results were also found by Lasnon et al. (1), who showed that PSF images resulted in higher heterogeneity than EARL-compliant images.

We found that the repeatability of most metrics was independent of the tracer uptake interval and reconstruction protocol, for each segmentation method evaluated. Moreover, MATV and other metrics were highly correlated, as well as their TRTs. This finding may seem to be inconsistent with the results of Hatt et al. (24), but we believe it can be explained by the use of different segmentation procedures and acquisition protocols. Moreover, to identify predictors of repeatability in MATV, the correlations of TRT_{MATV} with MATV and SUV_{max} were also investigated. We found that, in general, the repeatability of MATV was better with high values of MATV or SUV_{max}, suggesting that small lesions are more likely to be affected by variation in imaging procedures, consistent with our previous study (25).

As proposed by AAPM Report No. 211, accuracy evaluation of segmentation methods is required for each PET scanning condition (5). Our study confirms and further supports this recommendation. We observed that MATV, as well as most of the other metrics, depends not only on the segmentation method but more specifically on its specific combination with uptake interval and reconstruction protocol. In other words, methods and procedures that may work well under one condition may be outperformed by other methods under different conditions. Therefore, it seems that the selection of the best segmentation method is highly dependent on the imaging procedures and conditions at hand, confirming the AAPM recommendation to evaluate performances for each scanning condition. Despite the publication of strict imaging guidelines (10,26), there remains considerable variability in imaging procedures. To some extent, these are mitigated by scanner accreditation programs (27), but residual variability will likely remain and require implementation of the AAPM Report No. 211 recommendations.

The absence of ground truth in our study does not allow the accuracy of measured values to be assessed. In addition, although numerous data were included in our study to explore their interactions, these data were derived from [^{18}F]FDG PET images from only 10 NSCLC patients, which may not be sufficient to fully demonstrate their relationships in other clinical scenarios. Therefore, further studies are needed to establish a benchmark to evaluate their accuracy under different conditions.

CONCLUSION

Quantitative results derived from [^{18}F]FDG PET/CT studies on NSCLC patients show that all segmentation results need to be critically reviewed and that MATV, and other quantitative metrics, depend on segmentation method, uptake interval, and reconstruction protocol. Methods that perform well under one condition may not be suitable under different circumstances or studies. These interactions also suggest that to obtain quantitative reliable metrics with a good TRT performance, the optimal segmentation method depends on local imaging procedures, PET/CT systems, or reconstruction protocols used. Rigid harmonization of imaging procedures and PET/CT performance will be helpful in mitigating this variability (28-30).

DISCLOSURE

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TABLE 1. Patient characteristics.

Characteristics	Median	Scan 1	Scan 2	*P*
Patients	10			
Gender	Male: 6 Female: 4			
Age (years)	61 [45-66]			
Tumor type (histology)				
Adenocarcinoma	7			
Squamous cell carcinoma	3			
Tumor stage				
IIIb	3			
IV	7			
Tumor location	Lung			
Lesions per patient	2 [1-13]			
Weight (kg)		76 [57-110]	75 [57-113]	0.781
Number of patients (lesions)				
60 min uptake interval		10 (26)	10 (26)	
90 min uptake interval		10 (26)	8 (18)*	
Injected activity (MBq)		248 [194-377]	238 [192-392]	0.800
Scan start time (min)				
60 min uptake interval		61 [59-67]	60 [60-63]	0.293
90 min uptake interval		92 [90-97]	90 [90-95]	0.219

Data presented as median [range], *P*-values from Wilcoxon signed-rank test. *For two patients, the 90 min PET scans were not collected due to the inability to comply with the scan duration.

TABLE 2. Comparison of out of mask index for each segmentation method with different uptake interval and reconstruction protocols.

Uptake interval	Reconstruction	MASAC	AP	CAC	ST	41MAX	A50P	SUV25	SUV40
60 Min (%)	EARL	54	65	77	64	50	31	67	42
	ING	54	64	75	62	44	29	71	42
	PSF1	54	52	77	56	40	27	75	40
	PSF2	54	50	77	56	35	29	73	42
90 Min (%)	EARL	53	64	72	56	42	31	81	53
	ING	53	64	78	56	42	33	81	56
	PSF1	53	56	78	53	47	31	86	61
	PSF2	53	50	72	50	33	28	86	67
Total (%)		53	58	76	56	42	30	78	50

TABLE 3. Generalized Estimating Equations model, significance results (P-value) for all metrics tested.

Variable	Metrics	MASAC	AP	CAC	ST	41MAX	A50P	SUV25	SUV40
Uptake interval	MATV	0.215	**0.002**	0.386	**0.003**	**0.024**	0.213	**0.001**	**0.005**
	SUV_{max}	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	SUV_{mean}	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	TLG	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	CIH_{AUC}	0.433	0.569	**0.001**	0.065	0.143	0.115	**<0.001**	**<0.001**
	Homogeneity	**<0.001**	**<0.001**	0.134	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Entropy	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Dissimilarity	0.282	0.134	0.529	0.549	0.641	0.666	0.396	0.165
	HIE	0.086	0.201	**0.011**	0.441	0.239	0.390	**<0.001**	0.085
	ZP	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Reconstruction	MATV	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.122
	SUV_{max}	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	SUV_{mean}	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	TLG	**<0.001**	**<0.001**	**0.006**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**
	CIH_{AUC}	**<0.001**	0.156	**<0.001**	0.401	**0.002**	**<0.001**	**<0.001**	**<0.001**
	Homogeneity	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Entropy	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Dissimilarity	0.365	**<0.001**	**0.005**	**0.002**	**0.009**	0.143	0.716	0.138
	HIE	0.066	0.082	**<0.001**	0.927	0.524	**<0.001**	**<0.001**	0.297
	ZP	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Uptake interval × Reconstruction	MATV	0.624	0.210	0.373	0.233	0.138	0.158	**0.017**	0.223
	SUV_{max}	0.865	0.966	0.966	0.708	0.775	0.775	0.775	0.412
	SUV_{mean}	0.730	0.722	0.530	0.104	0.689	0.243	**0.042**	0.086
	TLG	0.552	0.102	0.620	0.294	0.071	0.230	**0.025**	0.241
	CIH_{AUC}	0.535	0.192	0.351	0.117	0.122	0.324	**0.031**	0.491
	Homogeneity	**0.008**	**<0.001**	**0.018**	0.050	0.225	**0.021**	**0.002**	**0.021**
	Entropy	0.107	**0.030**	**0.022**	0.090	0.268	**0.004**	**0.002**	0.339
	Dissimilarity	0.364	0.161	0.505	0.715	0.951	0.632	0.852	0.956
	HIE	0.793	0.349	0.374	**0.040**	0.099	0.207	0.429	0.550
	ZP	0.218	0.078	**0.007**	**0.040**	0.215	**0.041**	**0.001**	0.119

Statistically significant results (P<0.05) are presented in bold.

TABLE 4. Generalized Estimating Equations model, significance results (*P*-values) for all test-retest repeatability metrics tested.

Variable	TRT	MASAC	AP	CAC	ST	41MAX	A50P	SUV25	SUV40
Reconstruction	MATV	0.742	0.216	0.256	0.246	0.182	0.901	0.179	0.792
	SUV_{max}	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	SUV_{mean}	0.942	**0.018**	0.409	0.136	**0.016**	0.520	0.081	0.200
	TLG	0.614	0.602	0.166	0.371	0.652	0.928	0.288	0.737
	CIH_{AUC}	0.197	0.297	0.474	0.095	0.609	0.114	**0.007**	**0.022**
	Homogeneity	0.668	0.195	0.378	0.310	0.568	0.121	0.109	0.761
	Entropy	0.483	**0.030**	**0.041**	0.272	**0.040**	0.457	0.345	0.089
	Dissimilarity	0.493	0.388	0.605	0.261	0.550	0.221	0.562	0.417
	HIE	0.125	0.498	0.157	0.562	0.549	0.783	**0.036**	0.809
	ZP	0.197	0.452	0.775	0.340	0.602	0.235	0.069	0.731
Uptake interval × Reconstruction	MATV	0.307	0.082	0.579	0.524	0.924	0.121	0.058	0.908
	SUV_{max}	0.896	0.372	0.372	0.156	0.367	0.367	0.367	0.351
	SUV_{mean}	0.166	**0.022**	0.697	0.798	0.346	0.196	**0.035**	0.663
	TLG	0.309	0.121	0.661	0.301	0.872	0.119	0.158	0.913
	CIH_{AUC}	0.174	**0.048**	0.332	0.358	0.733	0.113	0.313	0.602
	Homogeneity	0.965	0.250	0.938	**0.038**	**0.009**	0.248	0.077	0.367
	Entropy	0.939	0.422	0.198	0.331	**0.023**	0.840	0.226	0.540
	Dissimilarity	0.534	0.926	0.902	0.362	0.712	0.572	0.421	0.567
	HIE	**0.045**	0.122	0.342	0.759	0.635	0.225	**0.047**	0.415
	ZP	0.530	0.585	0.948	0.467	0.523	0.403	0.795	0.347

Statistically significant results (*P*<0.05) are presented in bold.

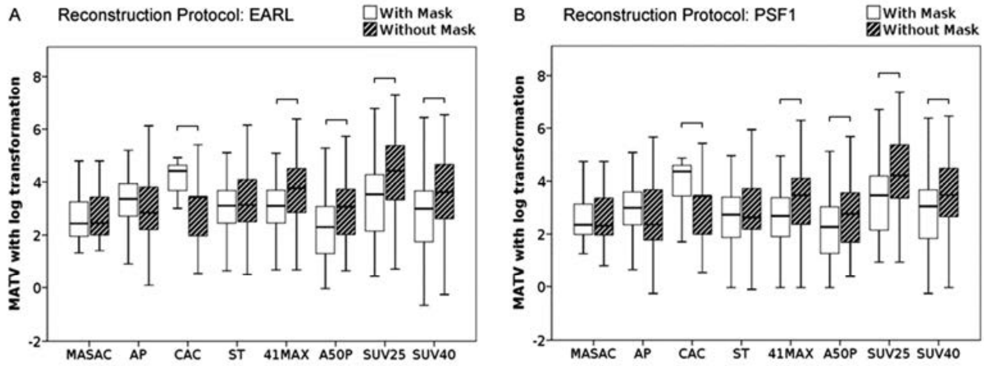

FIGURE 1. Box-and-whisker plots of MATV at 60 min for each segmentation method. For display purposes, outliers identified as 1.5 × inter-quartile range were removed from the plot (whiskers). Statistical significant differences are marked with a horizontal line.

3

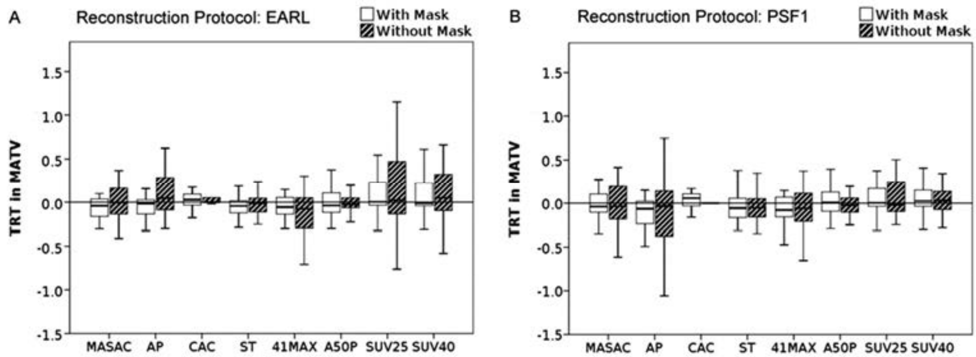

FIGURE 2. Box-and-whisker plots of TRT_{MATV} at 60 min for each segmentation method. For display purposes, outliers identified as 1.5 × inter-quartile range were removed from the plot (whiskers). No statistical significant differences were found.

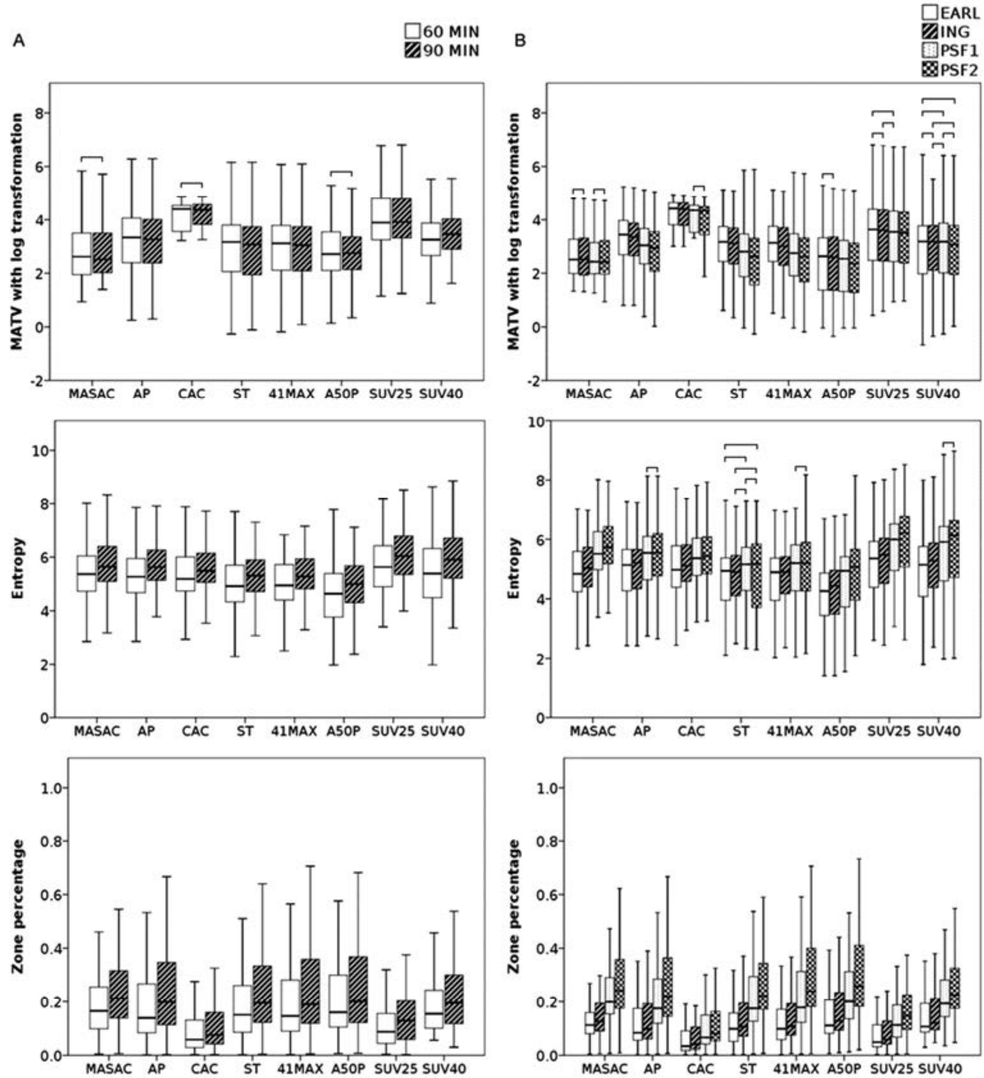

FIGURE 3. Box-and-whisker plots for various metrics as a function of uptake interval (A) and reconstruction protocol (B). For display purposes, outliers identified as 1.5 × inter-quartile range were removed from the plot (whiskers). Comparisons without statistical significant differences are marked with a horizontal line.

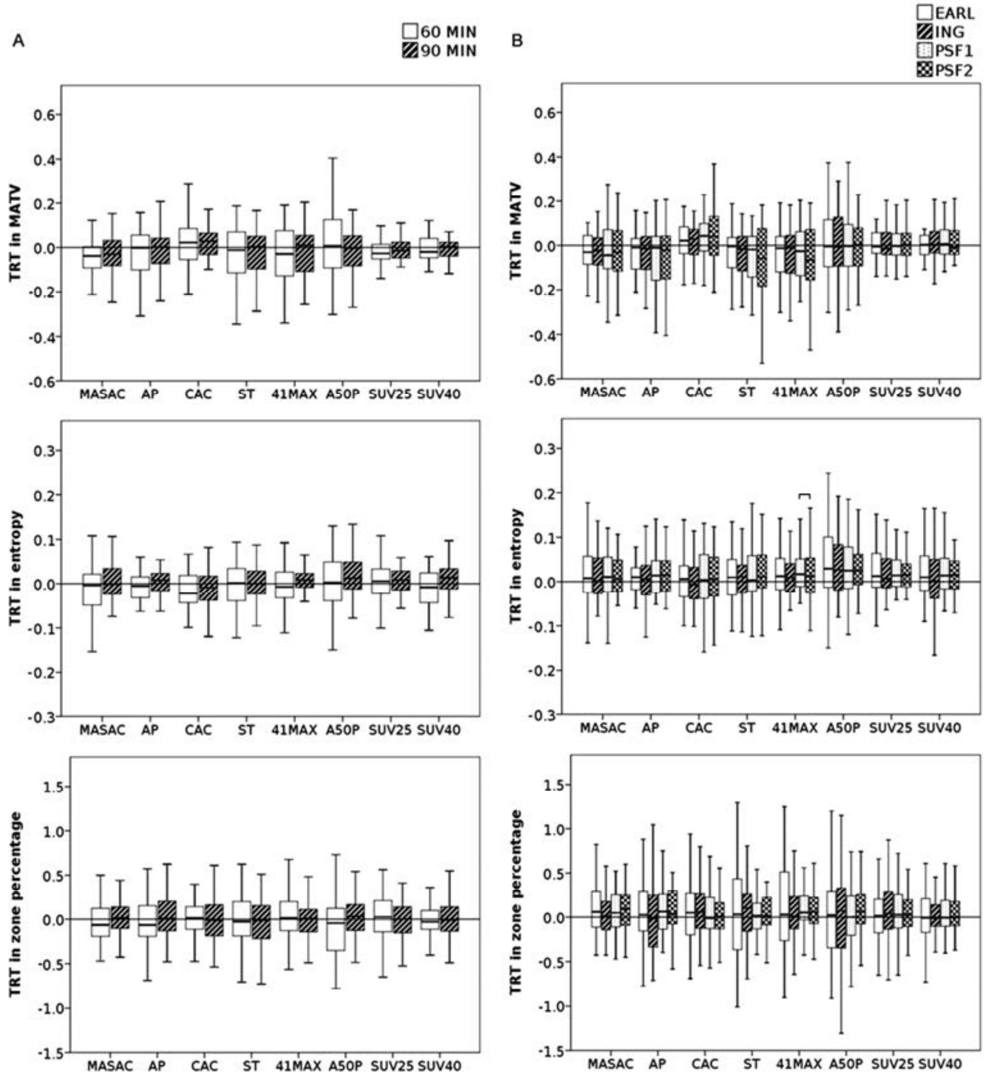

FIGURE 4. Box-and-whisker plots for TRT of various metrics as a function of uptake interval (A) and reconstruction protocol (B). For display purposes, outliers identified as 1.5 × inter-quartile range were removed from the plot (whiskers). Statistical significant differences are marked with a horizontal line.

3

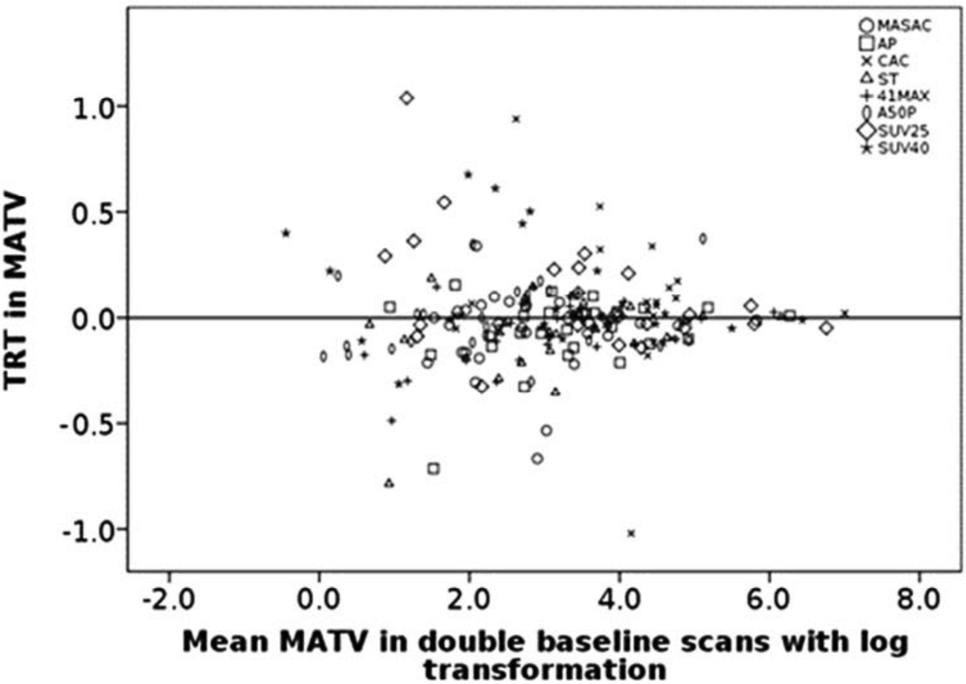

FIGURE 5. TRT_{MATV} as a function of MATV with the EARL reconstruction protocol at 60 min for each segmentation method.

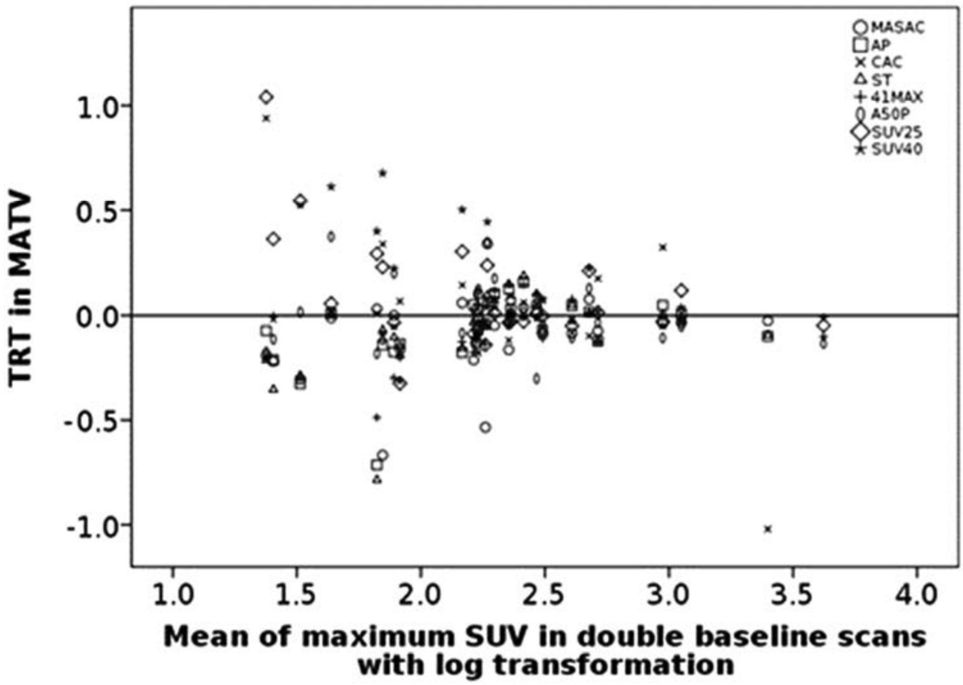

FIGURE 6. TRT_{MATV} as a function of SUV_{max} with the EARL reconstruction protocol at 60 min for each segmentation method.

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Supplemental Data Reconstruction

The default whole body reconstruction protocol on the Philips Ingenuity PET/CT (ING) is based on an iterative reconstruction using the ordered subset expectation maximization method. 3 iterations and 33 subsets are used and no post-reconstruction filtering is applied. The reconstructed images have a matrix size of 144×144 resulting in voxels of 4×4×4 mm.

The EARL compliant reconstruction is based on the same method and settings, but with a 4 mm full with half maximum (FWHM) Gaussian post-smoothing to achieve EARL compliance.

The PSF 1 and 2 reconstructions are also based on the ING reconstruction protocol, but now an iterative deconvolution method using the system's point spread function is applied with 1 or 2 iterations, respectively, to enhance the spatial resolution of the reconstructed images. All reconstruction methods and settings are provided by the vendor using predefined reconstruction protocols.

Supplemental Formulas for Local Heterogeneity Features

Homogeneity, entropy, and dissimilarity are derived from a gray level co-occurrence matrix (https://en.wikipedia.org/wiki/Co-occurrence_matrix).

$$homogeneity = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{p(i,j)}{1+|i-j|} \qquad \text{Eq. (1)}$$

$$entropy = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j) \log_2 \left(p(i,j)+\epsilon\right) \qquad \text{Eq. (2)}$$

$$dissimilarity = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} |i-j| p(i,j) \quad \text{Eq. (3)}$$

where N_g is the number of gray level intensities, and $p(i,j)$ is the (i,j) element in the normalized co-occurrence matrix, representing the number of times for the combination in which levels i and j occur in two pixels in the image, separated by a distance of δ pixels in direction α. In our study, N_g is set at 64 gray levels, and δ is 1 overall 13 spatial directions (26-connectivity in 3D).

High-intensity emphasis and zone percentage are calculated with a gray level size zone matrix (https://en.wikipedia.org/wiki/Gray_level_size_zone_matrix).

$$HIE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \mathbf{P}(i,j) i^2}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \mathbf{P}(i,j)} \quad \text{Eq. (4)}$$

$$ZP = \sum_{i=1}^{N_g} \sum_{j=1}^{N_s} \frac{\mathbf{P}(i,j)}{N_p} \quad \text{Eq. (5)}$$

where N_g is the number of gray level intensities, N_s is the number of discreet zone sizes, N_p is the number of voxels, and $P(i,j)$ represents the number of times for a gray level zone (connected voxels) that shares gray level i and size j in the image.

Supplemental Table 1. Summary of implementations for the segmentation methods.

Segmentation Method	Implementation
MASAC	Incorporate both histogram fuzzy C-means clustering and textural gradient information into an active contour model
AP	Select the optimal thresholding value by clustering the intensities with a novel similarity metric
CAC	Replace original images by smoothed and contourlet-transformed images to a deformable active contour model
ST	Contrast-oriented thresholding method derived from phantom measurements and validated in clinical data
41MAX	41% of maximum value within the tumor
A50P	50% of peak tumor value threshold, adapted for local background
SUV25	Absolute SUV = 2.5
SUV40	Absolute SUV = 4.0

Supplemental Table 2. Effect of uptake interval. Estimated marginal means between 60 min and 90 min (90 min – 60 min) for each segmentation method and metric. This table is related to the factor "Uptake interval" in Table 3. Data presented as mean ± standard error, with P<0.05 in bold (continued on the next page).

Metrics	MASAC	AP	CAC	ST
MATV	-0.029±0.024	**-0.063±0.020**	0.031±0.036	**-0.073±0.025**
SUV_{max}	**0.152±0.016**	**0.153±0.016**	**0.153±0.016**	**0.150±0.016**
SUV_{mean}	**0.141±0.010**	**0.157±0.014**	**0.092±0.015**	**0.160±0.014**
TLG	**0.112±0.028**	**0.094±0.016**	**0.123±0.033**	**0.087±0.019**
CIH_{AUC}	-0.447±0.570	0.169±0.297	**-1.621±0.491**	0.578±0.313
Homogeneity	**-0.024±0.003**	**-0.023±0.003**	-0.007±0.005	**-0.020±0.004**
Entropy	**0.366±0.041**	**0.324±0.044**	**0.291±0.038**	**0.272±0.051**
Dissimilarity	0.166±0.154	0.356±0.237	-0.080±0.127	0.135±0.225
HIE	-0.046±0.027	-0.041±0.032	**-0.060±0.023**	-0.018±0.024
ZP	**0.047±0.005**	**0.047±0.006**	**0.022±0.005**	**0.042±0.009**

Supplemental Table 2. Effect of uptake interval. Estimated marginal means between 60 min and 90 min (90 min – 60 min) for each segmentation method and metric. This table is related to the factor "Uptake interval" in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued).

Metrics	41MAX	A50P	SUV25	SUV40
MATV	**-0.051±0.022**	0.026±0.021	**0.066±0.020**	**0.177±0.063**
SUV_{max}	**0.150±0.016**	**0.150±0.016**	**0.150±0.016**	**0.150±0.016**
SUV_{mean}	**0.155±0.014**	**0.136±0.010**	**0.091±0.005**	**0.087±0.008**
TLG	**0.104±0.017**	**0.162±0.022**	**0.157±0.021**	**0.264±0.060**
CIH_{AUC}	0.290±0.198	-0.913±0.579	**-2.413±0.574**	**-3.403±0.774**
Homogeneity	**-0.021±0.003**	**-0.022±0.006**	**-0.020±0.005**	**-0.027±0.007**
Entropy	**0.291±0.038**	**0.368±0.046**	**0.426±0.032**	**0.529±0.049**
Dissimilarity	0.108±0.232	-0.111±0.256	-0.221±0.260	-0.355±0.256
HIE	-0.030±0.026	-0.034±0.039	**-0.101±0.027**	-0.042±0.024
ZP	**0.045±0.008**	**0.038±0.008**	**0.034±0.005**	**0.035±0.006**

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Supplemental Table 3. Effect of reconstruction protocol. Estimated marginal mean in different metrics for each segmentation method, reconstruction, and metric. This table is related to the factor "Reconstruction" in Table 3. Data presented as mean ± standard error, with P< 0.05 in bold (continued on the next page).

		MASAC			AP		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	0.017±0.009			**0.069±0.007**		
	PSF1	**0.069±0.016**	**0.052±0.014**		**0.322±0.029**	**0.254±0.024**	
	PSF2	**0.078±0.017**	**0.061±0.014**	0.009±0.007	**0.467±0.039**	**0.398±0.035**	**0.145±0.011**
SUV_{max}	ING	**-0.051±0.004**			**-0.051±0.004**		
	PSF1	**-0.234±0.017**	**-0.184±0.014**		**-0.236±0.017**	**-0.186±0.013**	
	PSF2	**-0.330±0.025**	**-0.279±0.021**	**-0.095±0.008**	**-0.333±0.024**	**-0.282±0.021**	**-0.097±0.008**
SUV_{mean}	ING	**-0.023±0.003**			**-0.046±0.004**		
	PSF1	**-0.127±0.009**	**-0.104±0.007**		**-0.225±0.017**	**-0.179±0.014**	
	PSF2	**-0.165±0.012**	**-0.142±0.010**	**-0.038±0.005**	**-0.317±0.025**	**-0.271±0.021**	**-0.092±0.008**
TLG	ING	-0.006±0.007			**0.022±0.005**		
	PSF1	**-0.058±0.016**	**-0.052±0.014**		**0.097±0.019**	**0.075±0.016**	
	PSF2	**-0.087±0.020**	**-0.081±0.017**	**-0.029±0.006**	**0.150±0.025**	**0.128±0.021**	**0.053±0.006**
CIH_{AUC}	ING	**1.620±0.184**			0.230±0.149		
	PSF1	**5.811±0.565**	**4.191±0.462**		0.529±0.609	0.299±0.474	
	PSF2	**8.707±0.745**	**7.087±0.654**	**2.896±0.254**	0.719±0.815	0.489±0.682	0.190±0.235
Homogeneity	ING	**0.013±0.002**			**0.010±0.002**		
	PSF1	**0.041±0.005**	**0.027±0.003**		**0.041±0.005**	**0.030±0.004**	
	PSF2	**0.054±0.006**	**0.040±0.004**	**0.013±0.002**	**0.051±0.008**	**0.041±0.006**	**0.011±0.003**
Entropy	ING	**-0.171±0.013**			**-0.077±0.013**		
	PSF1	**-0.604±0.050**	**-0.433±0.043**		**-0.313±0.066**	**-0.236±0.059**	
	PSF2	**-0.825±0.070**	**-0.654±0.063**	**-0.221±0.023**	**-0.359±0.103**	**-0.281±0.096**	-0.046±0.039
Dissimilarity	ING	0.095±0.150			-0.117±0.121		
	PSF1	-0.152±0.148	-0.247±0.142		**-1.024±0.245**	**-0.907±0.231**	
	PSF2	-0.146±0.166	-0.241±0.153	0.006±0.093	**-1.214±0.290**	**-1.098±0.290**	-0.191±0.134
HIE	ING	-0.010±0.016			-0.038±0.025		
	PSF1	0.037±0.027	0.047±0.021		0.023±0.047	0.061±0.039	
	PSF2	0.065±0.034	0.075±0.029	0.027±0.017	0.034±0.049	0.073±0.039	0.012±0.021
ZP	ING	**-0.021±0.003**			**-0.017±0.003**		
	PSF1	**-0.087±0.008**	**-0.067±0.006**		**-0.094±0.011**	**-0.077±0.009**	
	PSF2	**-0.128±0.011**	**-0.107±0.009**	**-0.041±0.004**	**-0.146±0.018**	**-0.128±0.016**	**-0.052±0.008**

Supplemental Table 3. Effect of reconstruction protocol. Estimated marginal mean in different metrics for each segmentation method, reconstruction, and metric. This table is related to the factor "Reconstruction" in Table 3. Data presented as mean ± standard error, with *P*< 0.05 in bold (continued on the next page).

		CAC			ST		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	**0.017±0.003**			**0.083±0.010**		
	PSF1	**0.104±0.021**	**0.088±0.021**		**0.368±0.030**	**0.285±0.022**	
	PSF2	**0.135±0.029**	**0.119±0.028**	0.031±0.012	**0.568±0.060**	**0.485±0.055**	**0.200±0.037**
SUV_{max}	ING	**-0.051±0.004**			**-0.051±0.004**		
	PSF1	**-0.236±0.017**	**-0.186±0.013**		**-0.236±0.017**	**-0.186±0.013**	
	PSF2	**-0.333±0.024**	**-0.282±0.021**	**-0.097±0.008**	**-0.318±0.025**	**-0.267±0.022**	**-0.082±0.014**
SUV_{mean}	ING	-0.005±0.003			**-0.049±0.005**		
	PSF1	**-0.038±0.012**	**-0.033±0.010**		**-0.239±0.019**	**-0.189±0.015**	
	PSF2	-0.041±0.016	-0.036±0.014	-0.003±0.005	**-0.334±0.027**	**-0.284±0.023**	**-0.095±0.008**
TLG	ING	**0.012±0.004**			**0.033±0.007**		
	PSF1	0.067±0.026	0.055±0.024		**0.129±0.017**	**0.096±0.013**	
	PSF2	0.094±0.037	0.083±0.035	0.028±0.015	**0.234±0.046**	**0.201±0.044**	**0.105±0.035**
CIH_{AUC}	ING	**1.506±0.100**			0.057±0.185		
	PSF1	**5.679±0.302**	**4.173±0.232**		-0.318±0.700	-0.375±0.545	
	PSF2	**8.064±0.470**	**6.558±0.392**	**2.385±0.189**	-1.306±1.319	-1.363±1.222	-0.988±0.959
Homogeneity	ING	0.005±0.002			**0.012±0.003**		
	PSF1	0.009±0.006	0.003±0.005		**0.036±0.008**	**0.024±0.006**	
	PSF2	0.007±0.008	0.001±0.006	-0.002±0.002	**0.041±0.011**	**0.030±0.010**	0.005±0.004
Entropy	ING	**-0.102±0.015**			**-0.069±0.018**		
	PSF1	**-0.305±0.047**	**-0.203±0.035**		-0.169±0.099	-0.099±0.087	
	PSF2	**-0.389±0.061**	**-0.287±0.048**	**-0.084±0.016**	-0.088±0.161	-0.019±0.150	0.080±0.074
Dissimilarity	ING	0.049±0.068			0.055±0.197		
	PSF1	0.118±0.128	0.069±0.130		**-0.674±0.243**	**-0.728±0.205**	
	PSF2	0.334±0.145	0.285±0.136	**0.216±0.064**	**-1.151±0.422**	**-1.206±0.434**	-0.477±0.388
HIE	ING	0.022±0.015			0.002±0.033		
	PSF1	**0.124±0.023**	**0.101±0.018**		0.027±0.054	0.026±0.039	
	PSF2	**0.171±0.032**	**0.148±0.026**	**0.047±0.016**	0.026±0.050	0.024±0.041	-0.001±0.031
ZP	ING	**-0.010±0.003**			**-0.027±0.007**		
	PSF1	**-0.040±0.007**	**-0.030±0.005**		**-0.101±0.015**	**-0.075±0.010**	
	PSF2	**-0.055±0.009**	**-0.045±0.007**	**-0.015±0.003**	**-0.148±0.020**	**-0.121±0.016**	**-0.047±0.008**

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Supplemental Table 3. Effect of reconstruction protocol. Estimated marginal mean in different metrics for each segmentation method, reconstruction, and metric. This table is related to the factor "Reconstruction" in Table 3. Data presented as mean ± standard error, with *P*< 0.05 in bold (continued on the next page).

		41MAX			A50P		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	**0.072±0.007**			0.003±0.014		
	PSF	**0.330±0.021**	**0.258±0.017**		**0.078±0.015**	**0.075±0.017**	
	PSF	**0.479±0.030**	**0.407±0.025**	**0.149±0.009**	**0.116±0.019**	**0.112±0.024**	**0.038±0.012**
SUV_{max}	ING	**-0.053±0.00**			**-0.053±0.00**		
	PSF	**-0.246±0.01**	**-0.194±0.01**		**-0.246±0.01**	**-0.194±0.01**	
	PSF	**-0.349±0.01**	**-0.296±0.01**	**-0.102±0.00**	**-0.349±0.01**	**-0.296±0.01**	**-0.102±0.00**
SUV_{mean}	ING	**-0.047±0.00**			**-0.030±0.00**		
	PSF	**-0.230±0.01**	**-0.182±0.01**		**-0.168±0.01**	**-0.138±0.00**	
	PSF	**-0.322±0.02**	**-0.275±0.02**	**-0.092±0.00**	**-0.231±0.01**	**-0.200±0.01**	**-0.063±0.00**
TLG	ING	**0.024±0.005**			-0.027±0.01		
	PSF	**0.100±0.015**	**0.076±0.011**		**-0.090±0.01**	**-0.063±0.01**	
	PSF	**0.157±0.020**	**0.133±0.016**	**0.057±0.006**	**-0.115±0.02**	**-0.088±0.02**	**-0.025±0.00**
CIH_{AUC}	ING	**0.304±0.106**			**1.475±0.190**		
	PSF	**0.983±0.314**	**0.679±0.240**		**5.124±0.262**	**3.649±0.241**	
	PSF	**1.567±0.456**	**1.263±0.382**	**0.585±0.159**	**7.583±0.354**	**6.108±0.348**	**2.459±0.185**
Homogeneit	ING	**0.010±0.003**			**0.017±0.005**		
	PSF	**0.040±0.006**	**0.030±0.005**		**0.052±0.008**	**0.035±0.005**	
	PSF	**0.051±0.008**	**0.041±0.006**	**0.011±0.003**	**0.065±0.009**	**0.048±0.006**	**0.012±0.002**
Entropy	ING	**-0.075±0.01**			**-0.159±0.02**		
	PSF	**-0.291±0.05**	**-0.216±0.05**		**-0.564±0.05**	**-0.405±0.03**	
	PSF	**-0.330±0.08**	**-0.256±0.08**	-0.039±0.03	**-0.743±0.07**	**-0.584±0.05**	**-0.179±0.02**
Dissimilarity	ING	0.090±0.165			0.353±0.423		
	PSF	-0.523±0.21	**-0.614±0.19**		-0.064±0.53	-0.417±0.27	
	PSF	-0.633±0.24	**-0.723±0.23**	-0.109±0.15	0.362±0.476	0.009±0.233	0.426±0.222
HIE	ING	0.027±0.032			0.029±0.024		
	PSF	0.004±0.040	-0.024±0.03		0.061±0.032	0.031±0.026	
	PSF	0.022±0.048	-0.005±0.04	0.019±0.031	**0.123±0.030**	**0.094±0.028**	**0.062±0.018**
ZP	ING	**-0.026±0.00**			**-0.023±0.00**		
	PSF	**-0.105±0.01**	**-0.080±0.01**		**-0.090±0.00**	**-0.067±0.00**	
	PSF	**-0.158±0.01**	**-0.132±0.01**	**-0.052±0.00**	**-0.146±0.01**	**-0.123±0.01**	**-0.056±0.00**

Supplemental Table 3. Effect of reconstruction protocol. Estimated marginal mean in different metrics for each segmentation method, reconstruction, and metric. This table is related to the factor “Reconstruction” in Table 3. Data presented as mean ± standard error, with *P*< 0.05 in bold (continued).

		SUV25			SUV40		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	0.010±0.004			-0.028±0.01		
	PSF	0.034±0.015	0.024±0.011		-0.076±0.04	-0.048±0.03	
	PSF	**0.059±0.019**	**0.049±0.015**	**0.025±0.005**	-0.013±0.05	0.014±0.046	0.063±0.037
SUV_{max}	ING	**-0.053±0.00**			**-0.052±0.00**		
	PSF	**-0.246±0.01**	**-0.194±0.01**		**-0.242±0.01**	**-0.190±0.01**	
	PSF	**-0.349±0.01**	**-0.296±0.01**	**-0.102±0.00**	**-0.327±0.02**	**-0.275±0.02**	**-0.085±0.01**
SUV_{mean}	ING	**-0.024±0.00**			**-0.023±0.00**		
	PSF	**-0.112±0.00**	**-0.088±0.00**		**-0.106±0.00**	**-0.083±0.00**	
	PSF	**-0.153±0.01**	**-0.128±0.00**	**-0.041±0.00**	**-0.139±0.01**	**-0.116±0.01**	**-0.033±0.00**
TLG	ING	**-0.014±0.00**			**-0.051±0.01**		
	PSF	**-0.078±0.01**	**-0.064±0.01**		**-0.182±0.04**	**-0.132±0.03**	
	PSF	**-0.094±0.02**	**-0.079±0.01**	**-0.016±0.00**	**-0.153±0.05**	-0.102±0.05	0.030±0.043
CIH_{AUC}	ING	**1.340±0.128**			**1.707±0.167**		
	PSF	**5.887±0.398**	**4.547±0.307**		**7.326±0.566**	**5.620±0.447**	
	PSF	**8.302±0.516**	**6.961±0.422**	**2.415±0.139**	**9.739±0.751**	**8.032±0.660**	**2.412±0.399**
Homogeneit	ING	**0.015±0.003**			0.011±0.004		
	PSF	**0.045±0.007**	**0.030±0.004**		**0.040±0.005**	**0.029±0.004**	
	PSF	**0.057±0.008**	**0.042±0.006**	**0.011±0.002**	**0.042±0.006**	**0.031±0.006**	0.002±0.004
Entropy	ING	**-0.165±0.01**			**-0.166±0.01**		
	PSF	**-0.643±0.02**	**-0.478±0.02**		**-0.683±0.04**	**-0.518±0.03**	
	PSF	**-0.854±0.04**	**-0.689±0.03**	**-0.211±0.01**	**-0.818±0.07**	**-0.652±0.06**	-0.135±0.05
Dissimilarity	ING	-0.004±0.20			0.509±0.298		
	PSF	-0.030±0.29	-0.026±0.19		0.745±0.336	0.237±0.327	
	PSF	0.093±0.271	0.096±0.163	0.122±0.119	0.951±0.471	0.443±0.473	0.206±0.201
HIE	ING	-0.018±0.07			0.016±0.019		
	PSF	0.151±0.083	**0.169±0.025**		0.068±0.036	0.053±0.029	
	PSF	**0.253±0.085**	**0.271±0.031**	**0.102±0.011**	0.072±0.040	0.056±0.035	0.004±0.019
ZP	ING	**-0.016±0.00**			**-0.019±0.00**		
	PSF	**-0.068±0.00**	**-0.052±0.00**		**-0.080±0.01**	**-0.061±0.00**	
	PSF	**-0.102±0.01**	**-0.086±0.00**	**-0.034±0.00**	**-0.119±0.01**	**-0.100±0.00**	**-0.039±0.00**

Supplemental Table 4. Effect of the interaction between uptake interval and reconstruction. Estimated marginal mean difference between 60 min and 90 min (90 min – 60 min) per reconstruction for each segmentation method and metric. This table is related to the factor “Uptake interval × Reconstruction” in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued on the next page).

Metrics	Reconstruction	MASAC	AP	CAC	ST
MATV	EARL	-0.038±0.034	**-0.103±0.029**	0.035±0.048	**-0.096±0.028**
	ING	-0.017±0.025	**-0.078±0.022**	0.030±0.048	**-0.072±0.027**
	PSF1	-0.032±0.027	-0.047±0.033	0.042±0.042	**-0.072±0.028**
	PSF2	-0.030±0.026	-0.024±0.039	0.019±0.034	-0.052±0.034
SUV_{max}	EARL	**0.153±0.015**	**0.153±0.015**	**0.153±0.015**	**0.154±0.015**
	ING	**0.154±0.015**	**0.154±0.015**	**0.154±0.015**	**0.155±0.015**
	PSF1	**0.152±0.017**	**0.153±0.017**	**0.153±0.017**	**0.154±0.017**
	PSF2	**0.149±0.019**	**0.152±0.019**	**0.152±0.019**	**0.138±0.024**
SUV_{mean}	EARL	**0.141±0.011**	**0.159±0.013**	**0.088±0.016**	**0.161±0.014**
	ING	**0.139±0.011**	**0.156±0.013**	**0.093±0.015**	**0.157±0.013**
	PSF1	**0.144±0.011**	**0.158±0.016**	**0.092±0.015**	**0.165±0.015**
	PSF2	**0.140±0.013**	**0.153±0.019**	**0.094±0.018**	**0.157±0.019**
TLG	EARL	0.102±0.036	0.056±0.025	0.123±0.047	0.065±0.023
	ING	**0.122±0.029**	**0.079±0.019**	0.124±0.047	**0.085±0.022**
	PSF1	**0.113±0.030**	**0.110±0.025**	**0.133±0.040**	**0.093±0.021**
	PSF2	**0.110±0.027**	**0.129±0.029**	**0.113±0.034**	**0.105±0.024**
CIH_{AUC}	EARL	-0.526±0.616	0.266±0.412	-2.170±0.724	0.337±0.437
	ING	-0.741±0.517	0.070±0.376	-1.804±0.608	0.069±0.329
	PSF1	-0.247±0.666	0.256±0.287	**-1.371±0.412**	0.682±0.313
	PSF2	-0.273±0.702	0.085±0.440	-1.137±0.397	1.222±0.767
Homogeneity	EARL	**-0.032±0.004**	**-0.038±0.006**	**-0.022±0.006**	**-0.035±0.007**
	ING	**-0.029±0.004**	**-0.036±0.005**	**-0.017±0.005**	**-0.032±0.005**
	PSF1	**-0.020±0.004**	**-0.014±0.003**	0.004±0.006	-0.009±0.006
	PSF2	**-0.014±0.004**	-0.001±0.008	0.007±0.007	-0.003±0.010
Entropy	EARL	**0.393±0.045**	**0.397±0.041**	**0.364±0.040**	**0.378±0.056**
	ING	**0.402±0.041**	**0.406±0.041**	**0.346±0.036**	**0.360±0.047**
	PSF1	**0.348±0.047**	**0.282±0.047**	**0.246±0.047**	**0.219±0.060**
	PSF2	**0.322±0.049**	0.212±0.082	**0.208±0.053**	0.133±0.096
Dissimilarity	EARL	-0.034±0.176	0.759±0.352	-0.026±0.156	0.121±0.267
	ING	0.117±0.239	0.374±0.301	0.073±0.141	0.276±0.354
	PSF1	0.267±0.207	0.168±0.255	-0.216±0.190	-0.121±0.282
	PSF2	0.314±0.224	0.122±0.350	-0.150±0.140	0.264±0.387
HIE	EARL	-0.051±0.031	0.042±0.058	-0.031±0.032	-0.102±0.039
	ING	-0.056±0.033	-0.065±0.039	-0.038±0.029	-0.070±0.052
	PSF1	-0.031±0.031	-0.080±0.053	-0.082±0.029	-0.016±0.036
	PSF2	-0.045±0.033	-0.059±0.046	-0.087±0.029	0.114±0.072
ZP	EARL	**0.036±0.006**	**0.028±0.008**	0.011±0.004	**0.034±0.008**
	ING	**0.041±0.007**	**0.044±0.008**	**0.019±0.005**	**0.038±0.009**
	PSF1	**0.054±0.007**	**0.059±0.008**	**0.027±0.006**	**0.055±0.009**
	PSF2	**0.058±0.010**	**0.056±0.014**	**0.031±0.007**	0.040±0.018

Supplemental Table 4. Effect of the interaction between uptake interval and reconstruction. Estimated marginal mean difference between 60 min and 90 min (90 min – 60 min) per reconstruction for each segmentation method and metric. This table is related to the factor "Uptake interval × Reconstruction" in Table 3. Data presented as mean ± standard error, with P<0.05 in bold (continued).

Metrics	Reconstruction	41MAX	A50P	SUV25	SUV40
MATV	EARL	**-0.092±0.026**	0.037±0.030	**0.102±0.025**	**0.200±0.067**
	ING	**-0.065±0.023**	0.052±0.027	**0.086±0.022**	**0.167±0.064**
	PSF1	-0.031±0.023	0.008±0.020	**0.045±0.021**	0.117±0.061
	PSF2	-0.014±0.034	0.006±0.022	0.032±0.025	**0.224±0.093**
SUV_{max}	EARL	**0.147±0.015**	**0.147±0.015**	**0.147±0.015**	**0.134±0.016**
	ING	**0.149±0.015**	**0.149±0.015**	**0.149±0.015**	**0.137±0.017**
	PSF1	**0.152±0.017**	**0.152±0.017**	**0.152±0.017**	**0.148±0.019**
	PSF2	**0.150±0.020**	**0.150±0.020**	**0.150±0.020**	**0.180±0.026**
SUV_{mean}	EARL	**0.159±0.014**	**0.132±0.011**	**0.086±0.005**	**0.076±0.008**
	ING	**0.155±0.013**	**0.132±0.010**	**0.089±0.005**	**0.077±0.008**
	PSF1	**0.154±0.015**	**0.140±0.010**	**0.094±0.006**	**0.089±0.009**
	PSF2	**0.150±0.019**	**0.138±0.013**	**0.094±0.006**	**0.106±0.014**
TLG	EARL	0.067±0.022	**0.169±0.028**	**0.188±0.026**	**0.276±0.066**
	ING	**0.090±0.019**	**0.185±0.027**	**0.175±0.023**	**0.243±0.063**
	PSF1	**0.122±0.018**	**0.148±0.022**	**0.139±0.022**	**0.206±0.060**
	PSF2	**0.136±0.024**	**0.145±0.023**	**0.126±0.025**	**0.330±0.094**
CIH_{AUC}	EARL	0.679±0.289	-1.226±0.588	**-3.162±0.618**	**-3.670±0.809**
	ING	0.332±0.236	-1.228±0.570	**-2.851±0.613**	**-3.544±0.818**
	PSF1	0.113±0.259	-0.640±0.648	**-2.020±0.593**	**-2.859±0.868**
	PSF2	0.036±0.300	-0.559±0.679	-1.618±0.654	**-3.538±0.995**
Homogeneity	EARL	**-0.035±0.006**	**-0.049±0.011**	**-0.039±0.008**	**-0.038±0.009**
	ING	**-0.029±0.005**	**-0.033±0.006**	**-0.030±0.006**	**-0.034±0.006**
	PSF1	-0.011±0.006	-0.008±0.009	-0.009±0.006	-0.014±0.007
	PSF2	-0.009±0.009	0.002±0.012	-0.000±0.008	-0.022±0.014
Entropy	EARL	**0.349±0.042**	**0.455±0.051**	**0.507±0.040**	**0.552±0.066**
	ING	**0.317±0.039**	**0.406±0.045**	**0.474±0.031**	**0.528±0.057**
	PSF1	**0.272±0.046**	**0.347±0.060**	**0.395±0.035**	**0.462±0.062**
	PSF2	0.226±0.075	**0.264±0.069**	**0.328±0.044**	**0.574±0.094**
Dissimilarity	EARL	0.187±0.262	0.389±0.609	-0.079±0.408	-0.360±0.373
	ING	0.190±0.371	-0.015±0.395	-0.200±0.311	-0.427±0.557
	PSF1	-0.035±0.345	-0.599±0.480	-0.399±0.371	-0.258±0.284
	PSF2	0.090±0.382	-0.218±0.397	-0.205±0.303	-0.377±0.355
HIE	EARL	-0.122±0.062	-0.022±0.058	0.022±0.121	-0.016±0.032
	ING	-0.027±0.057	-0.030±0.058	**-0.146±0.037**	-0.082±0.048
	PSF1	0.029±0.068	-0.072±0.034	-0.151±0.054	-0.019±0.027
	PSF2	-0.002±0.046	-0.010±0.039	-0.129±0.054	-0.050±0.039
ZP	EARL	**0.037±0.008**	0.023±0.009	**0.020±0.005**	0.020±0.008
	ING	**0.037±0.008**	**0.028±0.009**	**0.029±0.007**	**0.037±0.009**
	PSF1	**0.053±0.009**	**0.053±0.007**	**0.045±0.007**	**0.045±0.009**
	PSF2	**0.053±0.014**	0.047±0.017	**0.044±0.007**	**0.038±0.009**

Supplemental Table 5. Effect of the interaction between uptake interval and reconstruction. At 60 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor “Uptake interval × Reconstruction” in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued on the next page).

Metrics		MASAC			AP		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	0.028±0.018			**0.081±0.012**		
	PSF	0.072±0.030	0.045±0.023		**0.350±0.043**	**0.269±0.033**	
	PSF	0.082±0.032	0.054±0.025	0.010±0.014	**0.507±0.055**	**0.425±0.044**	**0.157±0.014**
SUV_{max}	ING	**-0.050±0.00**			**-0.050±0.00**		
	PSF	**-0.235±0.01**	**-0.185±0.01**		**-0.236±0.01**	**-0.186±0.01**	
	PSF	**-0.332±0.02**	**-0.282±0.01**	**-0.096±0.00**	**-0.334±0.02**	**-0.283±0.01**	**-0.097±0.00**
SUV_{mean}	ING	**-0.024±0.00**			**-0.048±0.00**		
	PSF	**-0.125±0.00**	**-0.101±0.00**		**-0.226±0.01**	**-0.178±0.01**	
	PSF	**-0.165±0.01**	**-0.141±0.01**	**-0.040±0.00**	**-0.320±0.02**	**-0.272±0.01**	**-0.094±0.00**
TLG	ING	0.004±0.015			**0.033±0.009**		
	PSF	-0.052±0.02	-0.057±0.02		**0.124±0.034**	**0.091±0.026**	
	PSF	-0.083±0.03	**-0.087±0.02**	-0.031±0.01	**0.186±0.042**	**0.153±0.034**	**0.062±0.010**
CIH_{AUC}	ING	**1.513±0.216**			0.131±0.151		
	PSF	**5.951±0.534**	**4.438±0.453**		0.523±0.556	0.392±0.432	
	PSF	**8.834±0.639**	**7.321±0.579**	**2.883±0.251**	0.628±0.786	0.497±0.665	0.105±0.270
Homogeneit	ING	**0.015±0.002**			**0.011±0.003**		
	PSF	**0.047±0.006**	**0.032±0.005**		**0.053±0.008**	**0.041±0.006**	
	PSF	**0.063±0.007**	**0.048±0.005**	**0.016±0.002**	**0.070±0.012**	**0.058±0.010**	**0.017±0.005**
Entropy	ING	**-0.167±0.01**			**-0.073±0.02**		
	PSF	**-0.627±0.04**	**-0.460±0.03**		**-0.371±0.05**	**-0.298±0.04**	
	PSF	**-0.861±0.06**	**-0.694±0.05**	**-0.234±0.02**	**-0.451±0.09**	**-0.379±0.08**	-0.080±0.03
Dissimilarity	ING	0.171±0.253			-0.310±0.17		
	PSF	-0.001±0.17	-0.172±0.22		**-1.319±0.26**	**-1.010±0.23**	
	PSF	0.028±0.212	-0.143±0.24	0.030±0.161	**-1.533±0.33**	**-1.224±0.33**	-0.214±0.20
HIE	ING	-0.012±0.02			-0.092±0.04		
	PSF	0.048±0.033	0.060±0.029		-0.038±0.05	0.054±0.044	
	PSF	0.068±0.036	0.080±0.031	0.020±0.020	-0.016±0.06	0.076±0.051	0.022±0.032
ZP	ING	**-0.018±0.00**			-0.009±0.00		
	PSF	**-0.078±0.01**	**-0.060±0.00**		**-0.078±0.01**	**-0.069±0.00**	
	PSF	**-0.117±0.01**	**-0.099±0.01**	**-0.039±0.00**	**-0.131±0.01**	**-0.122±0.01**	**-0.053±0.01**

Supplemental Table 5. Effect of the interaction between uptake interval and reconstruction. At 60 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor "Uptake interval × Reconstruction" in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued on the next page).

Metrics		CAC			ST		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	0.014±0.006			**0.095±0.014**		
	PSF	**0.108±0.034**	0.093±0.034		**0.380±0.034**	**0.285±0.022**	
	PSF	**0.127±0.035**	**0.113±0.034**	**0.019±0.006**	**0.590±0.060**	**0.495±0.052**	**0.210±0.035**
SUV_{max}	ING	**-0.050±0.00**			**-0.050±0.00**		
	PSF	**-0.236±0.01**	**-0.186±0.01**		**-0.236±0.01**	**-0.186±0.01**	
	PSF	**-0.334±0.02**	**-0.283±0.01**	**-0.097±0.00**	**-0.326±0.02**	**-0.276±0.01**	**-0.090±0.00**
SUV_{mean}	ING	-0.002±0.00			**-0.051±0.00**		
	PSF	-0.036±0.01	**-0.034±0.01**		**-0.237±0.01**	**-0.185±0.01**	
	PSF	-0.038±0.01	-0.036±0.01	-0.002±0.00	**-0.336±0.02**	**-0.284±0.02**	**-0.099±0.00**
TLG	ING	0.012±0.005			**0.044±0.010**		
	PSF	0.072±0.038	0.060±0.035		**0.143±0.024**	**0.100±0.016**	
	PSF	0.089±0.041	0.077±0.038	0.017±0.007	**0.254±0.046**	**0.211±0.042**	**0.111±0.031**
CIH_{AUC}	ING	**1.689±0.154**			-0.077±0.19		
	PSF	**6.078±0.328**	**4.389±0.280**		-0.146±0.61	-0.069±0.46	
	PSF	**8.581±0.425**	**6.892±0.354**	**2.502±0.143**	-0.864±1.04	-0.786±0.92	-0.718±0.63
Homogeneit	ING	**0.008±0.002**			**0.013±0.004**		
	PSF	0.022±0.008	0.014±0.006		**0.049±0.011**	**0.036±0.009**	
	PSF	0.021±0.010	0.013±0.008	-0.001±0.00	**0.058±0.015**	**0.044±0.012**	0.009±0.005
Entropy	ING	**-0.111±0.01**			**-0.078±0.02**		
	PSF	**-0.364±0.05**	**-0.254±0.03**		-0.248±0.09	-0.170±0.07	
	PSF	**-0.467±0.06**	**-0.356±0.05**	**-0.103±0.01**	-0.211±0.15	-0.133±0.13	0.037±0.069
Dissimilarity	ING	0.099±0.106			0.132±0.321		
	PSF	0.023±0.155	-0.076±0.19		-0.795±0.30	-0.927±0.33	
	PSF	0.272±0.155	0.173±0.181	**0.249±0.076**	-1.079±0.37	-1.211±0.41	-0.285±0.28
HIE	ING	0.019±0.022			0.017±0.044		
	PSF	**0.098±0.026**	**0.079±0.025**		0.070±0.064	0.052±0.059	
	PSF	**0.142±0.036**	**0.123±0.029**	0.044±0.018	0.134±0.078	0.116±0.080	0.064±0.046
ZP	ING	**-0.006±0.00**			-0.025±0.00		
	PSF	**-0.032±0.00**	**-0.026±0.00**		**-0.091±0.01**	**-0.066±0.01**	
	PSF	**-0.044±0.00**	**-0.039±0.00**	**-0.013±0.00**	**-0.145±0.02**	**-0.121±0.01**	**-0.054±0.00**

Supplemental Table 5. Effect of the interaction between uptake interval and reconstruction. At 60 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor "Uptake interval × Reconstruction" in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued on the next page).

Metrics		41MAX			A50P		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	**0.085±0.011**			0.011±0.023		
	PSF	**0.360±0.030**	**0.275±0.021**		**0.063±0.020**	0.053±0.023	
	PSF	**0.518±0.039**	**0.433±0.030**	**0.158±0.010**	**0.100±0.025**	0.089±0.033	**0.037±0.014**
SUV_{max}	ING	**-0.052±0.00**			**-0.052±0.00**		
	PSF	**-0.244±0.01**	**-0.193±0.00**		**-0.244±0.01**	**-0.193±0.00**	
	PSF	**-0.348±0.01**	**-0.296±0.01**	**-0.103±0.00**	**-0.348±0.01**	**-0.296±0.01**	**-0.103±0.00**
SUV_{mean}	ING	**-0.049±0.00**			**-0.030±0.00**		
	PSF	**-0.232±0.01**	**-0.183±0.01**		**-0.164±0.01**	**-0.134±0.00**	
	PSF	**-0.326±0.02**	**-0.277±0.01**	**-0.094±0.00**	**-0.227±0.01**	**-0.197±0.01**	**-0.064±0.00**
TLG	ING	**0.036±0.008**			-0.019±0.02		
	PSF	**0.128±0.023**	**0.092±0.016**		**-0.100±0.02**	**-0.081±0.02**	
	PSF	**0.192±0.029**	**0.156±0.022**	**0.064±0.008**	**-0.127±0.02**	**-0.108±0.02**	-0.027±0.01
CIH_{AUC}	ING	0.131±0.143			**1.474±0.267**		
	PSF	0.700±0.402	0.569±0.291		**5.417±0.375**	**3.943±0.288**	
	PSF	1.246±0.549	1.115±0.441	**0.546±0.165**	**7.917±0.486**	**6.443±0.414**	**2.500±0.198**
Homogeneit	ING	**0.013±0.003**			0.025±0.010		
	PSF	**0.052±0.011**	**0.039±0.009**		**0.073±0.016**	**0.048±0.008**	
	PSF	**0.064±0.013**	**0.051±0.010**	**0.012±0.004**	**0.090±0.017**	**0.065±0.009**	**0.018±0.003**
Entropy	ING	**-0.091±0.02**			**-0.184±0.03**		
	PSF	**-0.330±0.06**	**-0.239±0.05**		**-0.618±0.05**	**-0.434±0.03**	
	PSF	**-0.392±0.09**	**-0.301±0.08**	-0.062±0.03	**-0.839±0.06**	**-0.655±0.04**	**-0.221±0.02**
Dissimilarity	ING	0.092±0.311			0.151±0.725		
	PSF	-0.634±0.34	-0.726±0.35		-0.559±0.97	-0.709±0.46	
	PSF	-0.681±0.30	-0.773±0.31	-0.047±0.19	0.058±0.786	-0.092±0.30	0.617±0.430
HIE	ING	0.075±0.039			0.025±0.035		
	PSF	0.079±0.067	0.004±0.060		0.035±0.043	0.010±0.037	
	PSF	0.082±0.051	0.007±0.055	0.003±0.062	0.129±0.044	**0.103±0.033**	**0.093±0.020**
ZP	ING	**-0.026±0.00**			**-0.020±0.00**		
	PSF	**-0.097±0.01**	**-0.071±0.01**		**-0.075±0.01**	**-0.055±0.00**	
	PSF	**-0.150±0.01**	**-0.124±0.01**	**-0.053±0.00**	**-0.134±0.01**	**-0.114±0.01**	**-0.059±0.00**

Supplemental Table 5. Effect of the interaction between uptake interval and reconstruction. At 60 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor "Uptake interval × Reconstruction" in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued).

Metrics		SUV25			SUV40		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	0.002±0.007			-0.044±0.02		
	PSF	0.005±0.024	0.003±0.017		-0.117±0.06	-0.073±0.05	
	PSF	0.024±0.031	0.022±0.024	0.019±0.008	-0.001±0.07	0.043±0.074	0.116±0.076
SUV_{max}	ING	**-0.052±0.00**			**-0.051±0.00**		
	PSF	**-0.244±0.011**	**-0.193±0.00**		**-0.235±0.01**	**-0.184±0.01**	
	PSF	**-0.348±0.01**	**-0.296±0.01**	**-0.103±0.00**	**-0.304±0.02**	**-0.254±0.02**	-0.069±0.02
SUV_{mean}	ING	**-0.023±0.00**			**-0.023±0.00**		
	PSF	**-0.108±0.00**	**-0.085±0.00**		**-0.100±0.00**	**-0.078±0.00**	
	PSF	**-0.149±0.01**	**-0.126±0.00**	**-0.041±0.00**	**-0.124±0.01**	**-0.102±0.01**	-0.024±0.01
TLG	ING	**-0.021±0.00**			**-0.067±0.01**		
	PSF	**-0.103±0.02**	**-0.082±0.01**		**-0.217±0.06**	-0.150±0.05	
	PSF	**-0.125±0.02**	**-0.104±0.02**	**-0.022±0.00**	-0.125±0.08	-0.059±0.08	0.092±0.087
CIH_{AUC}	ING	**1.495±0.194**			**1.770±0.193**		
	PSF	**6.458±0.474**	**4.962±0.333**		**7.732±0.696**	**5.962±0.589**	
	PSF	**9.073±0.630**	**7.578±0.484**	**2.616±0.174**	**9.804±0.991**	**8.035±0.944**	2.073±0.748
Homogeneit	ING	**0.020±0.005**			0.013±0.007		
	PSF	**0.060±0.011**	**0.041±0.007**		**0.052±0.010**	**0.039±0.008**	
	PSF	**0.076±0.014**	**0.057±0.009**	**0.016±0.003**	**0.050±0.012**	**0.036±0.011**	-0.002±0.00
Entropy	ING	**-0.182±0.02**			**-0.177±0.01**		
	PSF	**-0.699±0.03**	**-0.517±0.02**		**-0.728±0.06**	**-0.551±0.06**	
	PSF	**-0.944±0.05**	**-0.762±0.03**	**-0.245±0.01**	**-0.807±0.118**	**-0.629±0.113**	-0.079±0.10
Dissimilarity	ING	-0.065±0.36			0.475±0.524		
	PSF	-0.190±0.53	-0.125±0.36		0.796±0.342	0.321±0.605	
	PSF	0.030±0.460	0.094±0.255	0.220±0.222	0.943±0.469	0.467±0.806	0.146±0.322
HIE	ING	-0.102±0.14			-0.018±0.02		
	PSF	0.064±0.160	**0.166±0.032**		0.067±0.041	0.084±0.051	
	PSF	0.177±0.163	**0.279±0.041**	**0.113±0.020**	0.055±0.051	0.072±0.057	-0.012±0.03
ZP	ING	**-0.012±0.00**			-0.011±0.00		
	PSF	**-0.056±0.00**	**-0.044±0.00**		**-0.067±0.01**	**-0.057±0.00**	
	PSF	**-0.091±0.01**	**-0.079±0.01**	**-0.035±0.00**	**-0.110±0.011**	**-0.099±0.00**	**-0.042±0.01**

Supplemental Table 6. Effect of the interaction between uptake interval and reconstruction. At 90 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor “Uptake interval × Reconstruction” in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued on the next page).

Metrics		MASAc			AP		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	0.006±0.005			**0.056±0.006**		
	PSF	**0.066±0.011**	**0.060±0.011**		**0.294±0.031**	**0.238±0.029**	
	PSF	**0.074±0.009**	**0.068±0.009**	0.008±0.005	**0.427±0.041**	**0.371±0.039**	**0.133±0.012**
SUV_{max}	ING	**-0.051±0.00**			**-0.051±0.00**		
	PSF	**-0.233±0.02**	**-0.182±0.01**		**-0.236±0.02**	**-0.185±0.01**	
	PSF	**-0.328±0.03**	**-0.277±0.02**	**-0.094±0.01**	**-0.332±0.02**	**-0.281±0.02**	**-0.096±0.01**
SUV_{mean}	ING	**-0.022±0.00**			**-0.045±0.00**		
	PSF	**-0.129±0.01**	**-0.107±0.00**		**-0.224±0.02**	**-0.179±0.01**	
	PSF	**-0.164±0.01**	**-0.142±0.01**	**-0.036±0.00**	**-0.314±0.03**	**-0.269±0.02**	**-0.090±0.01**
TLG	ING	**-0.016±0.00**			0.011±0.004		
	PSF	**-0.063±0.01**	**-0.047±0.01**		**0.070±0.016**	**0.059±0.017**	
	PSF	**-0.090±0.01**	**-0.075±0.01**	**-0.028±0.00**	**0.113±0.019**	**0.102±0.020**	**0.043±0.006**
CIH_{AUC}	ING	**1.728±0.214**			0.328±0.168		
	PSF	**5.672±0.665**	**3.944±0.551**		0.534±0.728	0.206±0.580	
	PSF	**8.581±0.929**	**6.853±0.824**	**2.909±0.336**	0.809±0.921	0.481±0.780	0.275±0.269
Homogeneit	ING	**0.012±0.002**			**0.009±0.002**		
	PSF	**0.034±0.005**	**0.023±0.003**		**0.028±0.004**	**0.019±0.003**	
	PSF	**0.045±0.006**	**0.033±0.005**	**0.010±0.002**	**0.033±0.006**	**0.023±0.006**	0.004±0.003
Entropy	ING	**-0.175±0.01**			**-0.082±0.01**		
	PSF	**-0.582±0.06**	**-0.407±0.05**		**-0.255±0.07**	-0.173±0.07	
	PSF	**-0.789±0.08**	**-0.614±0.07**	**-0.207±0.02**	-0.266±0.12	-0.184±0.12	-0.011±0.05
Dissimilarity	ING	0.019±0.100			0.076±0.183		
	PSF	-0.303±0.16	-0.322±0.14		-0.728±0.29	-0.804±0.30	
	PSF	-0.320±0.20	-0.340±0.17	-0.018±0.11	-0.896±0.38	-0.972±0.39	-0.168±0.21
HIE	ING	-0.008±0.02			0.015±0.035		
	PSF	0.027±0.027	0.035±0.022		0.084±0.069	0.068±0.051	
	PSF	0.062±0.038	0.070±0.036	0.035±0.020	0.085±0.059	0.070±0.042	0.001±0.026
ZP	ING	**-0.023±0.00**			**-0.025±0.00**		
	PSF	**-0.096±0.00**	**-0.073±0.00**		**-0.110±0.01**	**-0.084±0.01**	
	PSF	**-0.139±0.01**	**-0.116±0.01**	**-0.043±0.00**	**-0.160±0.02**	**-0.134±0.01**	**-0.050±0.01**

Supplemental Table 6. Effect of the interaction between uptake interval and reconstruction. At 90 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor "Uptake interval × Reconstruction" in Table 3. Data presented as mean ± standard error, with P<0.05 in bold (continued on the next page).

Metrics		CAC			ST		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	**0.019±0.004**			**0.071±0.011**		
	PSF	**0.101±0.026**	**0.082±0.025**		**0.356±0.033**	**0.285±0.026**	
	PSF	**0.144±0.041**	**0.125±0.041**	0.042±0.020	**0.546±0.066**	**0.475±0.061**	**0.190±0.040**
SUV_{max}	ING	**-0.051±0.00**			**-0.051±0.00**		
	PSF	**-0.236±0.02**	**-0.185±0.01**		**-0.236±0.02**	**-0.185±0.01**	
	PSF	**-0.332±0.02**	**-0.281±0.02**	**-0.096±0.01**	**-0.310±0.03**	**-0.259±0.02**	**-0.074±0.02**
SUV_{mean}	ING	-0.008±0.00			**-0.048±0.00**		
	PSF	-0.040±0.01	-0.032±0.01		**-0.241±0.02**	**-0.193±0.01**	
	PSF	-0.044±0.01	-0.036±0.01	-0.004±0.00	**-0.332±0.03**	**-0.284±0.02**	**-0.091±0.01**
TLG	ING	0.011±0.004			0.023±0.008		
	PSF	0.061±0.031	0.050±0.030		**0.115±0.016**	**0.092±0.013**	
	PSF	0.099±0.051	0.088±0.050	0.038±0.024	**0.214±0.051**	**0.191±0.050**	0.099±0.039
CIH_{AUC}	ING	**1.323±0.151**			0.191±0.224		
	PSF	**5.280±0.428**	**3.956±0.297**		-0.490±0.81	-0.681±0.65	
	PSF	**7.547±0.665**	**6.224±0.543**	**2.268±0.275**	-1.749±1.66	-1.939±1.58	-1.258±1.30
Homogeneit	ING	0.003±0.003			0.010±0.004		
	PSF	-0.004±0.00	-0.007±0.00		**0.023±0.007**	0.013±0.005	
	PSF	-0.008±0.00	-0.011±0.00	-0.003±0.00	0.025±0.011	0.015±0.010	0.002±0.006
Entropy	ING	**-0.093±0.01**			-0.060±0.01		
	PSF	**-0.246±0.05**	**-0.153±0.04**		-0.089±0.11	-0.029±0.10	
	PSF	**-0.311±0.06**	**-0.218±0.05**	**-0.065±0.01**	0.035±0.184	0.095±0.175	0.123±0.088
Dissimilarity	ING	-4.167±0.05			-0.023±0.16		
	PSF	0.214±0.156	0.214±0.130		-0.553±0.28	-0.530±0.20	
	PSF	0.397±0.169	0.397±0.134	0.183±0.098	-1.223±0.55	-1.200±0.53	-0.670±0.55
HIE	ING	0.026±0.018			-0.014±0.04		
	PSF	**0.149±0.033**	**0.123±0.023**		-0.016±0.05	-0.001±0.04	
	PSF	**0.199±0.037**	**0.173±0.031**	0.049±0.018	-0.082±0.04	-0.068±0.05	-0.066±0.04
ZP	ING	**-0.014±0.00**			-0.028±0.00		
	PSF	**-0.048±0.00**	**-0.034±0.00**		**-0.111±0.01**	**-0.083±0.01**	
	PSF	**-0.065±0.01**	**-0.051±0.00**	**-0.017±0.00**	**-0.151±0.02**	**-0.122±0.01**	**-0.039±0.01**

Supplemental Table 6. Effect of the interaction between uptake interval and reconstruction. At 90 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor "Uptake interval × Reconstruction" in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued on the next page).

Metrics		41MAX			A50P		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	**0.058±0.006**			-0.004±0.01		
	PSF	**0.300±0.019**	**0.242±0.017**		**0.093±0.018**	**0.097±0.015**	
	PSF	**0.440±0.030**	**0.382±0.028**	**0.141±0.013**	**0.131±0.020**	**0.135±0.022**	**0.038±0.013**
SUV_{max}	ING	**-0.053±0.00**			**-0.053±0.00**		
	PSF	**-0.249±0.01**	**-0.195±0.01**		**-0.249±0.01**	**-0.195±0.01**	
	PSF	**-0.350±0.02**	**-0.297±0.01**	**-0.102±0.00**	**-0.350±0.02**	**-0.297±0.01**	**-0.102±0.00**
SUV_{mean}	ING	**-0.045±0.00**			**-0.031±0.00**		
	PSF	**-0.227±0.01**	**-0.182±0.01**		**-0.172±0.01**	**-0.142±0.01**	
	PSF	**-0.318±0.02**	**-0.272±0.02**	**-0.091±0.01**	**-0.234±0.02**	**-0.203±0.01**	**-0.062±0.00**
TLG	ING	0.013±0.005			**-0.035±0.01**		
	PSF	**0.073±0.012**	**0.060±0.009**		**-0.080±0.02**	-0.045±0.01	
	PSF	**0.123±0.019**	**0.110±0.015**	**0.050±0.007**	**-0.103±0.02**	-0.068±0.02	-0.023±0.01
CIH_{AUC}	ING	**0.477±0.112**			**1.476±0.212**		
	PSF	**1.265±0.298**	**0.788±0.251**		**4.831±0.304**	**3.354±0.288**	
	PSF	**1.889±0.457**	**1.412±0.406**	0.624±0.211	**7.250±0.364**	**5.774±0.402**	**2.419±0.228**
Homogeneit	ING	0.007±0.004			**0.009±0.003**		
	PSF	**0.028±0.004**	**0.021±0.004**		**0.032±0.004**	**0.023±0.005**	
	PSF	**0.038±0.008**	**0.031±0.007**	0.010±0.004	**0.039±0.006**	**0.030±0.007**	0.007±0.003
Entropy	ING	-0.059±0.01			**-0.134±0.02**		
	PSF	**-0.253±0.06**	-0.194±0.06		**-0.510±0.07**	**-0.376±0.05**	
	PSF	-0.269±0.10	-0.210±0.10	-0.016±0.04	**-0.648±0.09**	**-0.513±0.08**	**-0.137±0.03**
Dissimilarity	ING	0.089±0.190			0.555±0.302		
	PSF	-0.412±0.26	-0.502±0.21		0.430±0.292	-0.124±0.20	
	PSF	-0.584±0.35	-0.673±0.31	-0.172±0.25	0.665±0.376	0.111±0.262	0.235±0.167
HIE	ING	-0.020±0.03			0.033±0.027		
	PSF	-0.072±0.07	-0.052±0.07		0.086±0.041	0.053±0.033	
	PSF	-0.038±0.06	-0.018±0.06	0.034±0.021	0.117±0.041	0.084±0.040	0.031±0.028
ZP	ING	**-0.026±0.00**			**-0.025±0.00**		
	PSF	**-0.114±0.01**	**-0.088±0.01**		**-0.105±0.01**	**-0.080±0.00**	
	PSF	**-0.165±0.02**	**-0.139±0.01**	**-0.052±0.01**	**-0.157±0.01**	**-0.132±0.01**	**-0.053±0.01**

Supplemental Table 6. Effect of the interaction between uptake interval and reconstruction. At 90 min uptake interval, estimated marginal mean difference between reconstruction protocols for each segmentation and metric. This table is related to the factor "Uptake interval × Reconstruction" in Table 3. Data presented as mean ± standard error, with *P*<0.05 in bold (continued).

Metrics		SUV25			SUV40		
		EARL	ING	PSF1	EARL	ING	PSF1
MATV	ING	**0.018±0.003**			-0.011±0.00		
	PSF	**0.063±0.011**	**0.045±0.009**		-0.034±0.03	-0.023±0.02	
	PSF	**0.094±0.013**	**0.076±0.011**	**0.031±0.004**	-0.025±0.04	-0.014±0.03	0.009±0.009
SUV_{max}	ING	**-0.053±0.00**			**-0.053±0.00**		
	PSF	**-0.249±0.01**	**-0.195±0.01**		**-0.249±0.01**	**-0.195±0.01**	
	PSF	**-0.350±0.02**	**-0.297±0.01**	**-0.102±0.00**	**-0.350±0.02**	**-0.297±0.01**	**-0.102±0.00**
SUV_{mean}	ING	**-0.026±0.00**			**-0.023±0.00**		
	PSF	**-0.116±0.008**	**-0.090±0.00**		**-0.113±0.009**	**-0.089±0.00**	
	PSF	**-0.157±0.01**	**-0.131±0.01**	**-0.041±0.00**	**-0.154±0.01**	**-0.131±0.011**	**-0.042±0.00**
TLG	ING	-0.008±0.00			**-0.034±0.00**		
	PSF	**-0.053±0.01**	**-0.046±0.01**		**-0.147±0.03**	**-0.113±0.027**	
	PSF	**-0.063±0.01**	**-0.055±0.01**	-0.010±0.00	**-0.180±0.04**	**-0.145±0.03**	**-0.033±0.00**
CIH_{AUC}	ING	**1.185±0.123**			**1.644±0.170**		
	PSF	**5.316±0.425**	**4.131±0.342**		**6.921±0.571**	**5.277±0.431**	
	PSF	**7.530±0.553**	**6.345±0.471**	**2.214±0.166**	**9.673±0.722**	**8.029±0.586**	**2.752±0.201**
Homogeneit	ING	**0.011±0.002**			**0.009±0.002**		
	PSF	**0.031±0.004**	**0.020±0.003**		**0.028±0.003**	**0.019±0.002**	
	PSF	**0.037±0.005**	**0.027±0.004**	**0.007±0.002**	**0.034±0.004**	**0.025±0.003**	**0.006±0.002**
Entropy	ING	**-0.148±0.00**			**-0.154±0.011**		
	PSF	**-0.587±0.02**	**-0.438±0.02**		**-0.638±0.03**	**-0.484±0.03**	
	PSF	**-0.764±0.04**	**-0.616±0.04**	**-0.178±0.01**	**-0.829±0.05**	**-0.675±0.05**	**-0.190±0.02**
Dissimilarity	ING	0.057±0.122			0.542±0.354		
	PSF	0.130±0.157	0.074±0.106		0.694±0.407	0.152±0.109	
	PSF	0.156±0.203	0.099±0.143	0.025±0.087	0.960±0.526	0.418±0.205	0.266±0.147
HIE	ING	**0.066±0.016**			0.049±0.036		
	PSF	**0.237±0.030**	**0.171±0.028**		0.070±0.037	0.021±0.026	
	PSF	**0.328±0.034**	**0.262±0.032**	**0.091±0.012**	0.089±0.041	0.040±0.032	0.019±0.015
ZP	ING	**-0.020±0.00**			**-0.028±0.00**		
	PSF	**-0.080±0.00**	**-0.060±0.00**		**-0.092±0.01**	**-0.065±0.00**	
	PSF	**-0.114±0.011**	**-0.093±0.00**	**-0.033±0.00**	**-0.128±0.01**	**-0.100±0.00**	**-0.036±0.00**

Supplemental Table 7. Test of GEE model significance results (*P*-values) on MATV with any other extracted metric as main effect (continued on the next page).

Variable	Metrics	MASAC	AP	CAC	ST	41MAX	A50P	SUV25	SUV40
Metric	SUV_{max}	**0.002**	**0.001**	0.072	**0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	SUV_{mean}	**0.004**	**0.003**	**0.011**	**0.020**	**0.001**	**<0.001**	**<0.001**	**<0.001**
	TLG	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	CIH_{AUC}	0.131	0.571	**<0.001**	0.414	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Homogeneity	**0.001**	**0.029**	**<0.001**	**0.012**	**0.031**	0.415	0.782	0.126
	Entropy	**<0.001**	**<0.001**	0.492	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Dissimilarity	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	HIE	0.471	0.050	0.374	**0.011**	**0.003**	**<0.001**	**0.004**	**<0.001**
	ZP	0.701	**0.009**	**<0.001**	**<0.001**	**0.014**	**0.013**	**0.003**	**<0.001**
Metric * Uptake time	SUV_{max}	**0.013**	0.061	0.589	0.115	0.063	0.367	0.800	0.079
	SUV_{mean}	**0.005**	**0.045**	0.785	0.171	0.070	0.242	0.764	**0.017**
	TLG	0.083	0.070	0.131	0.114	0.102	0.162	0.243	0.609
	CIH_{AUC}	0.274	0.926	0.395	0.479	**0.020**	0.609	0.395	0.924
	Homogeneity	0.229	0.215	0.757	0.177	0.149	0.222	0.206	**0.018**
	Entropy	**0.048**	**0.037**	0.609	**0.048**	**0.042**	0.354	**0.041**	0.711
	Dissimilarity	0.288	0.584	**0.047**	0.189	0.072	0.059	**0.017**	**0.041**
	HIE	0.170	0.486	0.390	0.081	0.149	0.277	0.324	0.822
	ZP	**0.004**	0.113	0.142	0.742	0.075	0.219	0.255	0.355

Supplemental Table 7. Test of GEE model significance results (*P*-values) on MATV with any other extracted metric as main effect (continued).

Variable	Metrics	MASAC	AP	CAC	ST	41MAX	A50P	SUV25	SUV40
Metric * Reconstruction	SUV_{max}	0.216	**<0.001**	0.356	**<0.001**	**<0.001**	**0.003**	**<0.001**	0.189
	SUV_{mean}	0.426	**0.001**	**<0.001**	**<0.001**	**<0.001**	**0.002**	**<0.001**	**0.036**
	TLG	**<0.001**	**<0.001**	**0.017**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.731
	CIH_{AUC}	0.543	0.358	**<0.001**	0.459	0.389	**<0.001**	**<0.001**	0.369
	Homogeneity	0.155	0.268	0.188	**0.016**	0.074	0.361	0.341	**0.001**
	Entropy	0.294	**0.011**	**0.025**	**0.020**	0.253	0.133	0.198	0.319
	Dissimilarity	0.063	0.140	**<0.001**	**0.021**	0.478	**0.001**	**0.002**	**0.031**
	HIE	0.069	0.938	**<0.001**	0.057	0.087	0.630	**<0.001**	0.112
	ZP	0.941	**0.023**	0.112	0.139	0.107	0.245	0.263	**0.002**
Metric * Uptake time * Reconstruction	SUV_{max}	0.754	0.407	0.925	0.075	**<0.001**	0.295	0.581	0.511
	SUV_{mean}	0.868	0.164	**0.002**	**0.044**	**0.006**	0.237	0.165	0.319
	TLG	0.240	0.432	0.229	**0.020**	**<0.001**	**0.001**	**0.049**	**0.037**
	CIH_{AUC}	0.169	0.771	**<0.001**	0.743	0.115	0.898	0.254	0.630
	Homogeneity	0.457	0.197	0.153	0.348	0.587	**0.043**	0.533	**0.025**
	Entropy	0.326	0.062	0.672	0.052	0.101	0.124	0.533	0.316
	Dissimilarity	0.799	0.189	0.837	0.344	0.159	0.271	0.323	0.117
	HIE	0.064	0.383	0.199	0.630	0.205	0.242	**0.001**	**0.006**
	ZP	0.588	**0.001**	0.794	**0.034**	0.181	**<0.001**	0.095	**0.022**

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Supplemental Table 8. Test of GEE model significance results (*P*-values) on the TRT_{MATV} with any other TRT as main effect (continued on the next page).

Variable	Metrics	MASAC	AP	CAC	ST	41MAX	A50P	SUV25	SUV40
TRT	SUV_{max}	0.239	**0.009**	0.476	**0.037**	**<0.001**	0.911	0.079	0.058
	SUV_{mean}	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.174	**<0.001**
	TLG	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	CIH_{AUC}	**<0.001**	0.287	**0.002**	**0.021**	0.584	**0.001**	**0.031**	**0.001**
	Homogeneity	**0.005**	0.142	**<0.001**	0.131	0.166	0.080	0.454	0.802
	Entropy	0.305	**0.011**	0.933	**0.002**	**<0.001**	0.065	0.526	**<0.001**
	Dissimilarity	**0.027**	0.462	**0.018**	0.410	**0.031**	**0.008**	0.403	0.764
	HIE	0.056	**0.016**	0.924	0.123	**0.001**	**0.024**	0.078	0.495
	ZP	**0.001**	0.061	**0.013**	0.275	**0.001**	**0.001**	**0.001**	**<0.001**
TRT * Uptake time	SUV_{max}	0.923	0.764	0.316	0.607	0.708	0.759	0.780	**0.033**
	SUV_{mean}	0.704	0.857	0.589	0.891	0.961	0.180	0.386	0.934
	TLG	0.649	0.072	0.675	0.132	0.190	**0.013**	0.119	0.865
	CIH_{AUC}	**0.034**	0.451	**0.036**	0.291	0.609	0.213	0.894	0.092
	Homogeneity	0.637	0.520	0.539	0.173	0.905	0.334	**<0.001**	0.963
	Entropy	0.208	**0.015**	0.856	**0.007**	0.206	0.575	0.239	**0.044**
	Dissimilarity	0.633	0.116	**0.048**	0.963	0.852	0.277	0.067	**<0.001**
	HIE	0.076	0.300	0.262	0.068	0.380	0.184	0.503	**0.036**
	ZP	0.426	0.873	0.990	0.095	0.566	0.275	0.184	0.169

Supplemental Table 8. Test of GEE model significance results (*P*-values) on the TRT_{MATV} with any other TRT as main effect (continued).

Variable	Metrics	MASAC	AP	CAC	ST	41MAX	A50P	SUV25	SUV40
TRT * Reconstruction	SUV_{max}	**0.016**	0.321	0.221	0.274	0.617	0.609	**0.016**	0.610
	SUV_{mean}	0.106	0.390	**<0.001**	0.921	0.790	0.573	**0.012**	0.166
	TLG	0.428	0.104	0.335	0.160	0.488	0.066	0.259	0.302
	CIH_{AUC}	0.349	**0.022**	0.475	0.430	0.104	**0.003**	**0.010**	0.626
	Homogeneity	0.406	**0.009**	0.112	**0.036**	0.334	0.083	**0.029**	**<0.001**
	Entropy	0.234	0.900	0.155	0.445	0.488	0.359	0.157	0.118
	Dissimilarity	0.421	0.129	0.171	0.319	0.091	0.146	0.060	0.158
	HIE	0.371	0.554	0.874	**0.026**	**0.041**	0.331	**0.002**	0.102
	ZP	0.762	0.574	0.439	0.414	**0.032**	0.280	0.473	0.073
TRT * Uptake time * Reconstruction	SUV_{max}	0.336	0.051	0.062	0.394	0.050	0.455	0.109	0.631
	SUV_{mean}	0.272	**0.045**	0.061	0.344	0.115	0.540	0.144	0.978
	TLG	0.860	0.695	0.192	0.673	0.516	0.106	0.369	0.274
	CIH_{AUC}	0.129	0.853	0.539	**0.009**	0.054	0.062	0.094	0.308
	Homogeneity	0.268	0.131	0.097	0.638	0.552	0.054	**0.001**	**<0.001**
	Entropy	0.418	0.576	**0.001**	**0.018**	0.270	0.450	0.122	0.259
	Dissimilarity	0.546	0.424	0.916	0.254	0.052	0.754	0.483	0.264
	HIE	0.842	**<0.001**	**0.044**	**<0.001**	0.114	**0.035**	0.280	**0.004**
	ZP	0.481	**0.002**	0.196	**0.001**	0.937	**<0.001**	0.388	0.176

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